Application for inclusion of a medicine in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion

Inclusion of desmopressin (DDAVP) for the treatment of select patients with von Willebrand disease, Hemophilia A and other rare bleeding disorders.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Blood & Transfusion Safety unit. WHO Designated Technical Officer: Junping Yu

3. Name of the organization(s) consulted and/or supporting the application

World Federation of Hemophilia.

4. International Nonproprietary Name (INN, generic name) of the medicine

INN: desmopressin; INN number: 3799

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Subcutaneous, intravenous, and intranasal.

6. International availability - sources, of possible manufacturers and trade names

Over 70 products manufactured or available in over 50 countries. See attached list, “Desmopressin NAMES”.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Therapeutic group.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Desmopressin is used in the treatment of select patients with hemophilia A or von Willebrand disease (VWD). Hemophilia A occurs in 1 in 5,000 male births. Ten percent of female carriers of hemophilia are also at risk of bleeding. (Source: National Center for Biotechnology Information, National Institutes of Health, United States.) VWD occurs with equal frequency among men and women, affecting up to 1% of the general population. Women are more likely to experience symptoms of VWD because of the increased bleeding it causes during their menstrual periods, during pregnancy, and after childbirth. (Source: United States Centers for Disease Control and Prevention.)

Desmopressin is currently used in the treatment of both bleeding disorders. It is recommended in the clinical guidelines of many national and international hematological organizations. (See for example, the attached documents “WFH 2013,” “UKHCDO 2014,” NHLBI 2008” and “ESA 2013.”)

Desmopressin may also be indicated in certain situations for patients with other coagulation disorders or platelet disorders. (Source: the attached document, “ESA 2013”)

Desmopressin is a safe and affordable alternative to plasma products and fresh blood components for patients with moderate and mild haemophilia, VWD and other hereditary bleeding disorders in the developed world and particularly in developing countries.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Desmopressin can be given through intravenous, subcutaneous and intranasal routes. The dose for both intravenous and subcutaneous routes is 0.3 mg/kg. The intranasal dose is 150 mg for patients weighing less than 50 kg and 300 mg for patients weighing more than 50 kg. (The intranasal solution of desmopressin used in the
treatment of bleeding disorders is more concentrated than that used in the treatment of nocturnal enuresis or diabetes insipidus.)


10. Summary of comparative effectiveness in a variety of clinical settings:

Clinical experience with desmopressin has greatly expanded over the past three decades. A review of the published literature affirms the efficacy and safety of desmopressin for prevention and treatment of bleeding in select patients with hemophilia A, VWD and other congenital bleeding disorders.

See the attached documents, “LEISSINGER 2014,” “MANNUCCI 1997” and “PGMJ 2007.”

11. Summary of comparative evidence on safety:

Most adverse events (AEs) associated with DDAVP are mild and related to the vasomotor effects of the drug (e.g. headache, facial flushing, mild hypotension and tachycardia). Mild to severe hyponatremia and hyponatremia-related seizures are the most serious AEs linked to the use of DDAVP and are caused by its antidiuretic effect, which is ten times greater with IV than with IN or SQ administration.

See the attached documents, “LEISSINGER 2014,” “MANNUCCI 1997” and “PGMJ 2007.”

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

Desmopressin is cost effective especially in comparison to blood derivatives and clotting factor concentrates. “Desmopressin is efficacious in mild hemophilia and type 1 VWD and usually permits the avoidance of concentrates, with significant reductions in costs. In the United States, for instance, an average dose of factor VIII concentrate (2,000 IU) costs between US$1,000 and $2,000. An average dose of desmopressin (21 µg) is much cheaper (US$100) and is even less expensive in Europe (the equivalent of US$20-$40).” (See the attached document “TOH 11 2012”)

13. Summary of regulatory status of the medicine (in various countries)

Desmopressin has regulatory approval in many countries including in Africa, Asia, Europe, North America and South America.


See attached document, “Ph EUR Desmopressin”.

15. Proposed (new/adapted) text that could be included in a revised WHO Model Formulary

Desmopressin: injection, 4 micrograms (acetate)/ml in 1-ml ampoule; nasal spray 10 micrograms (acetate)/metered dose
# Desmopressin names and manufacturers

## Generic Names

- Desmopressin (OS: BAN)
- Desmopressina (OS: DCIT)
- Desmopressine (OS: DCF)
- Desamino-Cys-D-Arg-Vasopressin (IS)
- UNII-ENR1LLB0FP (IS)
- Desmopressin (PH: BP 2011, Ph. Eur. 7)
- Desmopressine (PH: Ph. Eur. 7)
- Desmopressinum (PH: Ph. Eur. 7)
- Desmopressin Acetate (OS: BANM, USAN, JAN)
- DDAVP (IS)
- KW-8008 (IS)
- Minirin (IS)
- Stimate (IS)
- UNII-XB13HYU18U (IS)
- Desmopressin Acetate (PH: USP 34)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer, country</th>
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</thead>
<tbody>
<tr>
<td>1. Adiuretin</td>
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<tr>
<td>2. D.D.A.V.P.</td>
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</tr>
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<td>3. DDAVP</td>
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<td>4. Desmopresina Mede</td>
<td>Alfa Wassermann, Georgia; Reig Jofre, Spain</td>
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<td>6. D-Void</td>
<td>Sun, India</td>
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<td>7. Emosint</td>
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<td>15. Presinex</td>
<td>Kemofarmacij,a Slovenia</td>
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<td>16. Adin N</td>
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<td>21. Desmin</td>
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WFH GUIDELINES

Guidelines for the management of hemophilia

A. SRIVASTAVA,* A. K. BREWER,† E. P. MAUSER-BUNSCHOTEN,‡ N. S. KEY,§ S. KITCHEN,¶ A. LLINAS,** C. A. LUDLAM,†† J. N. MAHLANGU,‡‡ K. MULDER,§§ M. C. POON¶¶ and A. STREET***; TREATMENT GUIDELINES WORKING GROUP ON BEHALF OF THE WORLD FEDERATION OF HEMOPHILIA

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Summary. Hemophilia is a rare disorder that is complex to diagnose and to manage. These evidence-based guidelines offer practical recommendations on the diagnosis and general management of hemophilia, as well as the management of complications including musculoskeletal issues, inhibitors, and transfusion-transmitted infections. By compiling these guidelines, the World Federation of Hemophilia aims to assist healthcare providers seeking to initiate and/or maintain hemophilia care programs, encourage practice harmonization around the world and, where recommendations lack adequate evidence, stimulate appropriate studies.

Keywords: bleeding disorders, guidelines, hemophilia, management, treatment
### 5.4 THROAT AND NECK HEMORRHAGE

### 5.5 ACUTE GASTROINTESTINAL (GI) HEMORRHAGE

### 5.6 ACUTE ABDOMINAL HEMORRHAGE

### 5.7 OPHTHALMIC HEMORRHAGE

### 5.8 RENAL HEMORRHAGE

### 5.9 ORAL HEMORRHAGE

### 5.10 EPISTAXIS

### 5.11 SOFT TISSUE HEMORRHAGE

### 5.12 LACERATIONS AND ABRASIONS

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- Chronic hemophilic arthropathy
- Principles of physiotherapy/physical medicine in hemophilia
- Pseudotumors
- Fractures
- Principles of orthopedic surgery in hemophilia

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- Management of bleeding
- Allergic reactions in patients with hemophilia B
- Immune tolerance induction
- Patients switching to new concentrates

#### 6.3 TRANSFUSION-TRANSMITTED AND OTHER INFECTION-RELATED COMPLICATIONS
- Principles of management of HIV infection in hemophilia
- Principles of management of HCV infection in hemophilia
- Principles of management of HBV infection in hemophilia
- Principles of management of bacterial infection in hemophilia

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#### 7.1 CHOICE OF FACTOR REPLACEMENT THERAPY PROTOCOLS

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<td>Suggested plasma factor peak level and duration of administration (when there is no significant resource constraint)</td>
</tr>
<tr>
<td>7-2</td>
<td>Suggested plasma factor peak level and duration of administration (when there is significant resource constraint)</td>
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Introduction

The first edition of these guidelines, published in 2005 by the World Federation of Hemophilia (WFH), served its purpose of being a useful document for those looking for basic information on the comprehensive management of hemophilia. The need for revision has arisen for several reasons. The most significant of these was to incorporate the best existing evidence on which recommendations were based. There are recent high-quality data from randomized controlled trials establishing the efficacy and superiority of prophylactic factor replacement over episodic treatment – although the optimal dose and schedule for prophylaxis continue to be subjects of further research. There is also greater recognition of the need for better assessment of outcomes of hemophilia care using newly developed, validated, disease-specific clinicalmetric instruments. This revised version addresses these issues in addition to updating all sections.

These guidelines contain several recommendations regarding the clinical management of people with hemophilia (practice statements, in bold). All such statements are supported by the best available evidence in the literature, which were graded as per the 2011 Oxford Centre for Evidence-Based Medicine (Appendix I). Where possible, references for recommendations that fell outside the selection for practice statements were also included. These references have not been graded.

A question often raised when developing a guideline document such as this is its universal applicability, given the diversity of health services and economic systems around the world. Our strongly held view is that the principles of management of hemophilia are the same all over the world. The differences are mainly in the doses of clotting factor concentrates (CFC) used to treat or prevent bleeding, given that the costs of replacement products comprise the major expense of hemophilia care programs. Recognizing this reality, these guidelines continue to include a dual set of dose recommendations for CFC replacement therapy. These are based on published literature and practices in major centers around the world. It should be appreciated, however, that the lower doses recommended may not achieve the best results possible and should serve as the starting point for care to be initiated in resource-limited situations, with the aim of gradually moving toward more optimal doses, based on data and greater availability of CFC.

One of the reasons for the wide acceptance of the first edition of these guidelines was its easy reading format. While enhancing the content and scope of the document, we have ensured that the format has remained the same. We hope that it will continue to be useful to those initiating and maintaining hemophilia care programs. Furthermore, the extensive review of the literature and the wide consensus on which practice statements have been made may encourage practice harmonization around the world. More importantly, in areas where practice recommendations lack adequate evidence, we hope that this document will stimulate appropriate studies.
Section 1. General care and management of hemophilia

1.1 What is hemophilia?
1. Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (FIX) (in hemophilia B). The deficiency is the result of mutations of the respective clotting factor genes.
2. Hemophilia has an estimated frequency of approximately one in 10,000 births.
3. Estimations based on the WFH’s annual global surveys indicate that the number of people with hemophilia in the world is approximately 400,000 [1].
4. Hemophilia A is more common than hemophilia B, representing 80–85% of the total hemophilia population.
5. Hemophilia generally affects males on the maternal side. However, both F8 and F9 genes are prone to new mutations, and as many as 1/3 of all cases are the result of spontaneous mutation where there is no prior family history.
6. Accurate diagnosis of hemophilia is essential to inform appropriate management. Hemophilia should be suspected in patients presenting with a history of:
   • easy bruising in early childhood
   • “spontaneous” bleeding (bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues
   • Excessive bleeding following trauma or surgery
7. A family history of bleeding is obtained in about two-thirds of all patients.
8. A definitive diagnosis depends on factor assay to demonstrate deficiency of FVIII or FIX.

Bleeding manifestations
1. The characteristic phenotype in hemophilia is the bleeding tendency.
2. While the history of bleeding is usually life-long, some children with severe hemophilia may not have bleeding symptoms until later when they begin walking or running.
3. Patients with mild hemophilia may not bleed excessively until they experience trauma or surgery.
4. The severity of bleeding in hemophilia is generally correlated with the clotting factor level, as shown in Table 1-1.
5. Most bleeding occurs internally into the joints or muscles (see Tables 1-2 and 1-3).
6. Some bleeds can be life-threatening and require immediate treatment (see Section 5).

1.2 Principles of care
1. The primary aim of care is to prevent and treat bleeding with the deficient clotting factor.
2. Whenever possible, specific factor deficiency should be treated with specific factor concentrate.
3. People with hemophilia are best managed in a comprehensive care setting (see ‘Comprehensive Care’).
4. Acute bleeds should be treated as quickly as possible, preferably within 2 h. If in doubt, treat. (Level 4) [2]

Table 1-2. Sites of bleeding in hemophilia [63].

<table>
<thead>
<tr>
<th>Serious</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Joints (hemarthrosis)</td>
</tr>
<tr>
<td></td>
<td>Muscles, especially deep</td>
</tr>
<tr>
<td></td>
<td>compartments (iliopsoas,</td>
</tr>
<tr>
<td></td>
<td>calf, and forearm)</td>
</tr>
<tr>
<td></td>
<td>Mucous membranes in the</td>
</tr>
<tr>
<td></td>
<td>mouth, gums, nose, and</td>
</tr>
<tr>
<td></td>
<td>genitourinary tract</td>
</tr>
</tbody>
</table>

Table 1-3. Approximate frequency of bleeding at different sites.

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>Approximate frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemarthrosis</td>
<td>70–80</td>
</tr>
<tr>
<td>More common into hinged</td>
<td></td>
</tr>
<tr>
<td>joints: ankles, knees, and</td>
<td></td>
</tr>
<tr>
<td>elbows</td>
<td></td>
</tr>
<tr>
<td>Less common into multi-axial</td>
<td></td>
</tr>
<tr>
<td>joints: shoulders, wrists,</td>
<td></td>
</tr>
<tr>
<td>hips</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>10–20</td>
</tr>
<tr>
<td>Other major bleeds</td>
<td>5–10</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>&lt;5</td>
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</tbody>
</table>

Table 1-1. Relationship of bleeding severity with clotting factor level [62].

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clotting factor level</th>
<th>Bleeding episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1 IU dL⁻¹ (=0.01 IU mL⁻¹) or &lt;1% of normal</td>
<td>Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge</td>
</tr>
<tr>
<td>Moderate</td>
<td>1–5 IU dL⁻¹ (0.01–0.05 IU mL⁻¹) or 1–5% of normal</td>
<td>Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery</td>
</tr>
<tr>
<td>Mild</td>
<td>5–40 IU dL⁻¹ (0.05–0.40 IU mL⁻¹) or 5 to &lt;40% of normal</td>
<td>Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare</td>
</tr>
</tbody>
</table>
5. Patients usually recognize early symptoms of bleeding even before the manifestation of physical signs. This is often described as a tingling sensation or “aura”.

6. During an episode of acute bleeding, an assessment should be performed to identify the site of bleeding (if not clinically obvious) and appropriate clotting factor should be administered. In severe bleeding episodes that are potentially life-threatening, especially in the head, neck, chest, and gastrointestinal tract, treatment with factor should be initiated immediately, even before diagnostic assessment is completed.

7. To facilitate appropriate management in emergency situations, all patients should carry easily accessible identification, indicating the diagnosis, severity of the bleeding disorder, inhibitor status, type of treatment product used, initial dosage for treatment of severe, moderate, and mild bleeding, and contact information of the treating physician/clinic. (Level 5) [3]

8. Administration of desmopressin (DDAVP) can raise FVIII level adequately (three to six times baseline levels) to control bleeding in patients with mild, and possibly moderate, hemophilia A. Testing for DDAVP response in individual patients is appropriate. (Level 3) [4–6]

9. Veins must be treated with care. They are the lifelines for a person with hemophilia.

• 23- or 25-gauge butterfly needles are recommended.
• Never cut down into a vein, except in an emergency.
• Apply pressure for 3–5 min after venipuncture.
• Venous access devices should be avoided whenever possible, but may be required in some children.

Adjunctive therapies can be used to control bleeding, particularly in the absence of clotting factor concentrates, and may decrease the need for them (see ‘Adjunctive Management’).

12. If bleeding does not resolve despite adequate treatment, clotting factor levels should be measured. Inhibitor testing should be performed if the level is unexpectedly low (see ‘Inhibitor Testing’, and ‘Inhibitors’).

13. Prevention of bleeding can be achieved by prophylactic factor replacement (see ‘Prophylactic Factor Replacement Therapy’).

14. Home therapy can be used to manage mild/moderate bleeding episodes (see ‘Home therapy’).

15. Regular exercise and other measures to stimulate normal psychomotor development should be encouraged to promote strong muscles, develop balance and coordination, and improve fitness (see ‘Fitness and Physical Activity’).

16. Patients should avoid activities likely to cause trauma (see ‘Fitness and Physical Activity’).

17. Regular monitoring of health status and assessment of outcomes are key components of care (see ‘Monitoring Health Status and Outcome’).

18. Drugs that affect platelet function, particularly acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors, should be avoided. Paracetamol/acetaminophen is a safe alternative for analgesia (see ‘Pain Management’).

19. Factor levels should be raised to appropriate levels prior to any invasive procedure (see ‘Surgery and Invasive Procedures’).

20. Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding (see ‘Dental Care and Management’).

1.3 Comprehensive care

1. Comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality. (Level 3) [7–9]

2. Hemophilia is a rare disorder that is complex to diagnose and to manage. Optimal care of these patients, especially those with severe forms of the disease, requires more than the treatment of acute bleeding.

3. Priorities in the improvement of health and quality of life of people with hemophilia include:

• prevention of bleeding and joint damage
• prompt management of bleeding
• management of complications including:
  o joint and muscle damage and other sequelae of bleeding
  o inhibitor development
  o viral infection(s) transmitted through blood products
• attention to psychosocial health

Comprehensive care team

1. The wide ranging needs of people with hemophilia and their families are best met through the coordinated delivery of comprehensive care by a multidisciplinary team of healthcare professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available. (Level 5) [10–12]

2. The comprehensive care team should be multidisciplinary in nature, with expertise and experience to attend to the physical and psychosocial health of patients and their families.

3. The core team should consist of the following members:
• a medical director (preferably a pediatric and/or adult hematologist, or a physician with interest and expertise in hemostasis)
• a nurse coordinator who:
  ○ coordinates the provision of care
  ○ educates patients and their families
  ○ acts as the first contact for patients with an acute problem or who require follow-up
  ○ is able to assess patients and institute initial care where appropriate
• a musculoskeletal expert (physiotherapist, occupational therapist, physiatrist, orthopedist, rheumatologist) who can address prevention as well as treatment
• a laboratory specialist
• a psychosocial expert (preferably a social worker, or a psychologist) familiar with available community resources

4. The roles assumed by core team members may differ, depending on the availability and expertise of trained staff and the organization of services within the center.
5. All members of the core team should have expertise and experience in treating bleeding disorders and should be accessible to patients in a timely and convenient manner. Adequate emergency care should be available at all times.
6. The following support resources are necessary:
• Access to a coagulation laboratory capable of performing accurate and precise clotting factor assays and inhibitor testing.
• Provision of appropriate clotting factor concentrates, either plasma-derived or recombinant, as well as other adjunct hemostatic agents such as desmopressin (DDAVP) and tranexamic acid where possible.
• Where clotting factor concentrates are not available, access to safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate.
• Access to casting and/or splinting for immobilization and mobility/support aids, as needed.
7. The comprehensive care team should also include or have access to, among others:
• chronic pain specialist
• dentist
• geneticist
• hepatologist
• infectious disease specialist
• immunologist
• gynecologist/obstetrician
• vocational counselor
8. Written management protocols are required to ensure continuity of care despite changes in clinic personnel.
9. The comprehensive care team should have the resources to support family members. This may include identifying resources and strategies to help cope with:
• risks and problems of everyday living, particularly with management of bleeding
• changes associated with different stages of the patient’s growth and development (especially adolescence and aging)
• issues regarding schooling and employment
• risk of having another affected child and the options available
10. Establishing a long-term relationship between patients/families and members of the comprehensive care team promotes compliance.

Functions of a comprehensive care program

1. To provide or coordinate inpatient (i.e., during hospital stays) and outpatient (clinic and other visits) care and services to patients and their family.

• Patients should be seen by all core team members at least yearly (children every 6 months) for a complete hematologic, musculoskeletal, and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan. Referrals for other services can also be given during these visits. (Level 5) [13,14]
• The management plan should be developed with the patient and communicated to all treaters and care facilities. Communication among treaters is important.
• Smaller centers and personal physicians can provide primary care and management of some complications, in frequent consultation with the comprehensive care center (particularly for patients who live a long distance from the nearest hemophilia treatment center).

2. To initiate, provide training for, and supervise home therapy with clotting factor concentrates where available.
3. To educate patients, family members and other caregivers to ensure that the needs of the patient are met.
4. To collect data on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment, and surgical procedures. This information is best recorded in a computerized registry and should be updated regularly by a designated person and maintained in accordance with confidentiality laws and other national regulations. Systematic data collection will:
1.4 Fitness and physical activity

1. Physical activity should be encouraged to promote physical fitness and normal neuromuscular development, with attention paid to muscle strengthening, coordination, general fitness, physical functioning, healthy body weight, and self-esteem. (Level 2) [15]

2. Bone density may be decreased in people with hemophilia. [16,17]

3. For patients with significant musculoskeletal dysfunction, weight-bearing activities that promote development and maintenance of good bone density should be encouraged, to the extent their joint health permits. (Level 3) [16]

4. The choice of activities should reflect an individual’s preference/interests, ability, physical condition, local customs, and resources.

5. Non-contact sports such as swimming, walking, golf, badminton, archery, cycling, rowing, sailing, and table tennis should be encouraged.

6. High contact and collision sports such as soccer, hockey, rugby, boxing, and wrestling, as well as high-velocity activities such as motocross racing and skiing, are best avoided because of the potential for life-threatening injuries, unless the individual is on good prophylaxis to cover such activities.

7. Organized sports programs should be encouraged as opposed to unstructured activities, where protective equipment and supervision may be lacking.

8. The patient should consult with a musculoskeletal professional before engaging in physical activities to discuss their appropriateness, protective gear, prophylaxis (factor and other measures), and physical skills required prior to beginning the activity. This is particularly important if the patient has any problem/target joints [18].

9. Target joints can be protected with braces or splints during activity, especially when there is no clotting factor coverage. (Level 4) [19,20]

10. Activities should be re-initiated gradually after a bleed to minimize the chance of a re-bleed.

1.5 Adjunctive management

1. Adjunctive therapies are important, particularly where clotting factor concentrates are limited or not available, and may lessen the amount of treatment product required.

2. First aid measures: In addition to increasing factor level with clotting factor concentrates (or desmopressin in mild hemophilia A), protection (splint), rest, ice, compression, and elevation (PRICE) may be used as adjunctive management for bleeding in muscles and joints.

3. Physiotherapy/rehabilitation is particularly important for functional improvement and recovery after musculoskeletal bleeds and for those with established hemophilic arthropathy (see ‘Principles of Physiotherapy/Physical Medicine in Hemophilia’).

4. Antifibrinolytic drugs (e.g., tranexamic acid, epsilon aminocaproic acid) are effective as adjunctive treatment for mucosal bleeds and dental extractions (see ‘Tranexamic Acid’ and ‘Aminocaproic Acid’).

5. Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis (see ‘Pain Management’).

1.6 Prophylactic factor replacement therapy

1. Prophylaxis is the treatment by intravenous injection of factor concentrate to prevent anticipated bleeding (Table 1-4).

2. Prophylaxis was conceived from the observation that moderate hemophilia patients with clotting factor level > 1 IU dL\(^{-1}\) seldom experience...
spontaneous bleeding and have much better preservation of joint function. [21–24]

3. Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2) [24–29]

4. Prophylactic replacement of clotting factor has been shown to be useful even when factor levels are not maintained above 1 IU dL\(^{-1}\) at all times [26,29,30].

5. It is unclear whether all patients should remain on prophylaxis indefinitely as they transition into adulthood. Although some data suggest that a proportion of young adults can do well off prophylaxis [31], more studies are needed before a clear recommendation can be made. [32]

6. In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4–8 weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis. (Level 3) [33,34]

7. Prophylaxis does not reverse established joint damage; however, it decreases frequency of bleeding and may slow progression of joint disease and improve quality of life.

8. Prophylaxis as currently practiced in countries where there are no significant resource constraints is an expensive treatment and is only possible if significant resources are allocated to hemophilia care. However, it is cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.

9. In countries with significant resource constraints, lower doses of prophylaxis given more frequently may be an effective option.

10. Cost-efficacy studies designed to identify minimum dosage are necessary to allow access to prophylaxis in more of the world.

**Administration and dosing schedules**

1. There are two prophylaxis protocols currently in use for which there are long-term data:
   - The Malmö protocol: 25–40 IU kg\(^{-1}\) per dose administered three times a week for those with hemophilia A, and twice a week for those with hemophilia B.
   - The Utrecht protocol: 15–30 IU kg\(^{-1}\) per dose administered three times a week for those with hemophilia A, and twice a week for those with hemophilia B.

2. However, many different protocols are followed for prophylaxis, even within the same country, and the optimal regimen remains to be defined.

3. The protocol should be individualized as much as possible based on age, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates.

4. One option for the treatment of very young children is to start prophylaxis once a week and escalate depending on bleeding and venous access.

5. Prophylaxis is best given in the morning to cover periods of activity.

6. Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury. (Level 4) [18,34,35]

**1.7 Home therapy**

1. Where appropriate and possible, persons with hemophilia should be managed in a home therapy setting.

2. Home therapy allows immediate access to clotting factor and hence optimal early treatment, resulting in decreased pain, dysfunction, and long-term disability and significantly decreased hospital admissions for complications. (Level 3) [36,37]

3. Further improvements in quality of life include greater freedom to travel and participate in physical activities, less absenteeism, and greater employment stability. [38]

4. Home therapy is ideally achieved with clotting factor concentrates or other lyophilized products that are safe, can be stored in a domestic fridge, and are reconstituted easily.

5. Home treatment must be supervised closely by the comprehensive care team and should only be initiated after adequate education and training. (Level 3) [36,37]

6. Teaching should focus on general knowledge of hemophilia; recognition of bleeds and common complications; first aid measures; dosage calculation; preparation, storage, and administration of clotting factor concentrates; aseptic techniques; performing venipuncture (or access of central venous catheter); record keeping; proper storage and disposal of needles/sharps; and handling of blood spills. A certification program is helpful.

7. Patients or parents should keep bleed records (paper or electronic) that include date and site of bleeding, dosage and lot number of product used, and adverse effects

8. Infusion technique and bleed records should be reviewed and monitored at follow-up visits.

9. Home care can be started with young children with adequate venous access and motivated family members who have undergone adequate
training. Older children and teenagers can learn self-infusion with family support.

10. An implanted venous access device (Port-A-Cath) can make injections much easier and may be required for administering prophylaxis in younger children. (Level 2) [39,40]

11. However, the risks of surgery, local infection, and thrombosis associated with such devices need to be weighed against the advantages of starting intensive prophylaxis early. (Level 2) [41,42]

12. The venous access device must be kept scrupulously clean and be adequately flushed after each administration to prevent clot formation. [41]

1.8 Monitoring health status and outcome

1. Regular standardized evaluation at least every 12 months allows longitudinal assessment for individual patients and can identify new or potential problems in their early stages so that treatment plans can be modified. (Level 3) [14,26,43]

2. Patients should be seen by the multidisciplinary care team after every severe bleeding episode.

3. The following should be evaluated and education should be reviewed and reinforced:
   - issues related to venous access
   - issues related to hemostasis (bleed record)
   - use of products for replacement therapy and the response to them
   - musculoskeletal status: impairment and function through clinical assessment of joints and muscles, and radiological evaluation annually or as indicated (see ‘Musculoskeletal complications’)
   - transfusion-transmitted infections: commonly HIV, HCV, and HBV, and others if indicated (see ‘Transfusion-transmitted and other infection-related complications’)
   - development of inhibitors (see ‘Inhibitors’)
   - overall psychosocial status
   - dental/oral health

4. Several hemophilia-specific scores are available to measure joint impairment and function, including activities and participation. These include:
   - Impairment:
     - Clinical: WFH Physical Examination Score (aka Gilbert score), Hemophilia Joint Health Score (HJHS)
     - Radiological: Pettersson score, MRI, and ultrasound scores Activity: Haemophilia Activities List (HAL), Paediatric Haemophilia Activities List (PedHAL), Functional Independence Score in Hemophilia (FISH)
   - Health-related quality of life: (HaemoQol, Canadian Hemophilia Outcomes: Kids’ Life Assessment Tool [CHO-KLAT])

For more information on available functional and physical examination scores, see the WFH’s Compendium of Assessment Tools at: www.wfh.org/assessment_tools.

1.9 Pain management

Acute and chronic pain are common in patients with hemophilia. Adequate assessment of the cause of pain is essential to guide proper management.

**Pain caused by venous access**

1. In general, no pain medication is given.
2. In some children, application of a local anesthetic spray or cream at the site of venous access may be helpful.

**Pain caused by joint or muscle bleeding**

1. While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain control (Table 15).
2. Other measures include cold packs, immobilization, splints, and crutches [44].

**Postoperative pain**

1. Intramuscular injection of analgesia should be avoided.
2. Postoperative pain should be managed in coordination with the anesthesiologist.
3. Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine, hydrocodone, and others.
4. When pain is decreasing, paracetamol/acetaminophen may be used.

**Pain due to chronic hemophilic arthropathy**

1. Chronic hemophilic arthropathy develops in patients who have not been adequately treated with clotting factor concentrates for joint bleeding.
2. Treatment includes functional training, adaptations, and adequate analgesia as suggested in Table 15. (Level 2) [15,45]
3. COX-2 inhibitors have a greater role in this situation. (Level 2) [46,47]
4. Other NSAIDs should be avoided. (Level 2) [48]
5. When pain is disabling, orthopedic surgery may be indicated. (Level 5) [49]
6. Patients with persisting pain should be referred to a specialized pain management team.
be used with caution in patients with hypertension and renal dysfunction. Painkillers, under the supervision of a physician. COX-2 inhibitors should be used with caution in patients with hypertension and renal dysfunction.

Notes: If for any reason medications have been stopped for a period of time, patients who have been taking and tolerating high-dose narcotic medications may require additional planning and interaction with the healthcare team.

3. Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times per day.

Table 1-5. Strategies for pain management in patients with hemophilia.

<table>
<thead>
<tr>
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<th>Paracetamol/acetaminophen</th>
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<tbody>
<tr>
<td>1</td>
<td>If not effective ↓</td>
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<tr>
<td>2</td>
<td>COX-2 inhibitor (e.g., celecoxib, meloxicam, nimesulide, and others; OR Paracetamol/acetaminophen plus codeine (3–4 times per day) OR Paracetamol/acetaminophen plus tramadol (3–4 times per day)</td>
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</table>

1. Paracetamol/acetaminophen

2. COX-2 inhibitor (e.g., celecoxib, meloxicam, nimesulide, and others; OR Paracetamol/acetaminophen plus codeine (3–4 times per day) OR Paracetamol/acetaminophen plus tramadol (3–4 times per day)

3. Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times per day.

1.10 Surgery and invasive procedures

Surgery may be required for hemophilia-related complications or unrelated diseases. The following issues are of prime importance when performing surgery on persons with hemophilia:

1. Surgery for patients with hemophilia will require additional planning and interaction with the healthcare team than what is required for other patients.

2. A hemophilia patient requiring surgery is best managed at or in consultation with a comprehensive hemophilia treatment center. (Level 3) [50,51]

3. The anesthesiologist should have experience treating patients with bleeding disorders.

4. Adequate laboratory support is required for reliable monitoring of clotting factor level and inhibitor testing.

5. Preoperative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected. (Level 4) [52,53]

6. Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.

7. Adequate quantities of clotting factor concentrates should be available for the surgery itself and to maintain adequate coverage postoperatively for the length of time required for healing and/or rehabilitation.

8. If clotting factor concentrates are not available, adequate blood bank support for plasma components is needed.

9. The dosage and duration of clotting factor concentrate coverage depend on the type of surgery performed (Tables 7-1, 7-2).

10. Effectiveness of hemostasis for surgical procedures may be judged as per criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (Table 1-6).

11. Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks postoperatively. (Level 4) [54]

12. Careful monitoring for inhibitors is also advisable in patients with non-severe hemophilia A receiving continuous infusion after surgery [55].

13. Infusion of factor concentrates/hemostatic agents is necessary before invasive diagnostic procedures such as lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy.

1.11 Dental care and management

1. For persons with hemophilia, good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding [56].

2. Dental examinations should be conducted regularly, starting at the time the baby teeth start to erupt.

Table 1-6. Definition of adequacy of hemostasis for surgical procedures [64].

| Excellent | Intra-operative and postoperative blood loss similar (within 10%) to the non-hemophilic patient. | No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND Blood component transfusions required are similar to non-hemophilic patient |
| Good | Intra-operative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10 and 25% of expected), but the difference is judged by the involved surgeon/anaesthetist to be clinically insignificant | No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND Blood component transfusions required are similar to non-hemophilic patient |
| Fair | Intra-operative and/or postoperative blood loss increased over expectation (25–50%) for the non-hemophilic patient and additional treatment is needed | Extra (unplanned) dose of FVIII/FIX/bypassing agents factor needed OR Increased blood component (within 2 fold) of the anticipated transfusion requirement |
| Poor/none | Significant intra-operative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia | Unexpected hypotension or unexpected transfer to ICU due to bleeding OR Substantially increased blood component (>2 fold) of the anticipated transfusion requirement |

*Apart from estimates of blood loss during surgery, data on pre- and post-operative hemoglobin levels and the number of packed red blood cell units transfused may also be used, if relevant, to estimate surgical blood loss.

*Surgical hemostasis should be assessed by an involved surgeon and/or anaesthetist and records should be completed within 72 hours following surgery.

*Surgical procedures may be classified as major or minor. A major surgical procedure is defined as one that requires hemostatic support for periods exceeding 5 consecutive days.
3. Teeth should be brushed twice a day with a medium texture brush to remove plaque deposits.
4. Dental floss or interdental brushes should be used wherever possible.
5. Toothpaste containing fluoride should be used in areas where natural fluoride is not present in the water supply. Fluoride supplements may also be prescribed if appropriate.
6. An orthodontic assessment should be considered for all patients between the ages of 10–14 to determine if there are any problems associated with overcrowding, which can result in periodontal disease if left untreated.
7. Close liaison between the dental surgeon and the hemophilia team is essential to provide good comprehensive dental care.
8. Treatment can be safely carried out under local anesthesia using the full range of techniques available to dental surgeons. Infiltration, intra-epithelial, and intra-angular injections are often done under factor cover (20–40%) although it may be possible for those with adequate experience to administer these injections without it. (Level 4) [57,58]
9. Treatment from the hemophilia unit may be required before an inferior alveolar nerve block or lingual infiltration.
10. Dental extraction or surgical procedures carried out within the oral cavity should be performed with a plan for hemostasis management, in consultation with the hematologist. (Level 3) [51]

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Section 2. Special management issues

2.1 Carriers

1. Hemophilia is an X-linked disorder that typically affects males, while females are carriers.
2. Obligate carriers are:
   - daughters of a person with hemophilia
   - mothers of one son with hemophilia and who have at least one other family member with hemophilia
   - mothers of one son with hemophilia and who have a family member who is a known carrier of the hemophilia gene
   - mothers of two or more sons with hemophilia
3. The expected mean clotting factor level in carriers of hemophilia is 50% of the levels found in the healthy population [1,2].
4. Most carriers are asymptomatic.
5. Carriers with clotting factor levels of 40–60% of normal may have an increased bleeding tendency [3].
6. A few carriers may have clotting factor levels in the hemophilia range – mostly in the mild category – but in rare instances, carriers can be in the moderate or severe range due to extreme lyonization. (Table 1-1)
7. Carriers with clotting factor levels in the hemophilia range may be symptomatic with bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery [3].
8. Menorrhagia and bleeding after medical interventions are the most common manifestations among carriers with significantly low factor levels [3].
9. Carriers with low clotting factor levels should be categorized as having hemophilia of appropriate severity and managed accordingly.
10. Birth control pills and antifibrinolytic agents are useful in controlling symptoms of menorrhagia.
11. Levels of factor VIII increase significantly in pregnancy. Levels of factor IX, however, do not usually change significantly [4].
12. Immediate female relatives (mother, sisters, and daughters) of a person with hemophilia should have their clotting factor level checked, especially prior to any invasive intervention, childbirth, or if any symptoms occur. (Level 3) [3,5]

2.2 Genetic testing/counseling and prenatal diagnosis

1. Where available and possible, genetic testing for carrier status should be offered to at-risk female family members of people with hemophilia to facilitate genetic counseling, and if desired by the family, prenatal diagnosis. (Level 4) [6]
2. DNA-based mutation analysis to identify the specific mutation responsible for hemophilia in a particular family is becoming technically easier and more widely available. This facilitates identification of carriers and prenatal diagnosis for male fetuses.
3. Genetic counseling is key to helping people with hemophilia, carriers, and their families make more informed choices.
4. Prenatal diagnosis is usually offered when termination of the pregnancy would be considered if an affected fetus was identified. However, it may also be done to help the family prepare and to plan delivery. Assisted delivery is best avoided in an affected fetus.
5. Fetal gender can be determined using Y chromosome-specific PCR in maternal plasma/serum after 7–9 weeks of gestation [7,8] or by ultrasonography beginning week 11 of gestation [9].
6. Chorionic villus sampling (CVS), or biopsy, is the main method of prenatal diagnosis and is best done between 9 and 14 weeks of gestation. Biopsy carried out earlier may be associated with increased complications including fetal limb abnormalities. (Level 1) [10–13]
8. It is important to be aware of and to follow the relevant laws governing such procedures in the country where the service is being provided.
9. For carriers with low factor levels (<50 IU dL⁻¹), hemostatic support may be required to prevent maternal bleeding during prenatal diagnosis procedures.
10. All invasive methods used for prenatal diagnosis may cause feto-maternal hemorrhage. Anti-D immunoglobulin should be given if the mother is RhD negative. (Level 3) [14]
11. Preimplantation genetic diagnosis allows selection of embryos without specific mutation to be implanted into the uterus. [15]

2.3 Delivery of infants with known or suspected hemophilia

1. FVIII levels usually rise into the normal range during the second and third trimesters and should therefore be measured in carriers during the third trimester of pregnancy to inform decisions for factor coverage during delivery. (Level 3) [4]
2. In carriers with significantly low factor levels (<50 IU dL\(^{-1}\)), clotting factor replacement is necessary for surgical or invasive procedures including delivery. (Level 3) [4]
3. The need for clotting factor replacement should be planned in the prenatal period.
4. Route of delivery in carriers with a normal fetus should be as per obstetric indications.
5. Delivery of infants with known or suspected hemophilia should be atraumatic, regardless of whether it is vaginal or cesarean, to decrease the risk of bleeding. (Level 3) [4]
6. Forceps and vacuum extraction should be avoided in vaginal delivery, as well as invasive procedures to the fetus such as fetal scalp blood sampling and internal fetal scalp electrodes [16].

2.4 Vaccinations
1. Persons with bleeding disorders should be vaccinated, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless covered by infusion of clotting factor concentrates. (Level 4) [17]
2. If intramuscular injection is to be given:
   - It is best done soon after a dose of factor replacement therapy.
   - An ice pack can be applied to the injection area for 5 min before injection.
   - The smallest gauge needle available (usually 25–27 gauge) should be used.
   - Pressure should be applied to the injection site for at least 5 min [18].
3. Live virus vaccines (such as oral polio vaccine, MMR) may be contraindicated in those with HIV infection.
4. People with hemophilia who have HIV should be given pneumococcal and annual influenza vaccines.
5. Immunization to hepatitis A and hepatitis B is important for all persons with hemophilia. These immunizations may not be as effective in those with HIV infection. (Level 4) [19,20]

2.5 Psychosocial issues
1. Patients and their families should be provided with psychological and social support [21,22].
2. Hemophilia is also a financial burden that places restrictions on several aspects of normal living [23].
3. The social worker and/or other members of the comprehensive care team should:
   - provide as much information as possible about the physical, psychological, emotional, and economic dimensions of hemophilia, in terms the patient/parents can understand.
   - be open and honest about all aspects of care.
   - allow the patient/parents to work through their emotions and ask questions. Provide care and support patiently.
   - talk to affected children, not just their parents. Children can often understand a good deal about their illness and can work with the physician if properly informed and educated.
   - remind parents not to ignore siblings that are healthy.
   - be able to recognize warning signs of burnout and depression, which are common with chronic illness, and provide suggestions for coping.
   - recognize that cultural background may affect patients’ views of illness.
   - encourage patients to engage in productive and leisure activities at home and in the workplace.
   - work in partnership with the patient organization to advocate for hemophilia care and to provide education to families and members of the community.
   - enlist the assistance of local groups and organizations where social workers are unavailable.

2.6 Sexuality
1. Patients with hemophilia can have normal sexual intercourse [24].
2. Muscle bleedings (e.g., iliopsoas) may sometimes be the result of sexual activity.
3. Complications of hemophilia can be accompanied by sexual dysfunction, which may include lack of libido or impotence.
4. Pain or fear of pain may affect sexual desire, and hemophilic arthropathy may place limitations on sexual intercourse.
5. Sexuality is also affected by chronic HCV and HIV infection, age-related diseases like hypertension and diabetes mellitus, and certain medications.
6. In some cases, oral phosphodiesterase-5 inhibitors (sildenafil, tadalafil) may be helpful. These medications mildly inhibit platelet aggregation in vitro, and may cause epistaxis due to nasal congestion.

2.7 Aging hemophilia patients
1. Aging patients with hemophilia will inevitably suffer from age-related diseases [24,25].
2. Comorbidities in aging hemophilia patients should be managed appropriately as they may accentuate problems associated with hemophilia and impact the patient’s physical and psychosocial health, and thus their quality of life.

**Osteoporosis**
1. Bone mineral density (BMD) is decreased in people with hemophilia [26,27].
2. An increased number of arthropathic joints, loss of joint movement, and muscle atrophy leading to inactivity are associated with a lower BMD [27].
3. Weight-bearing activities (suitable sports) that promote development and maintenance of good bone density should be encouraged if joint health permits.
4. Calcium and vitamin D supplementation are also important and bisphosphonate therapy may be required. A dental evaluation is advisable before initiating long-term bisphosphonate therapy [28,29].

**Obesity**
1. The prevalence of overweight (BMI 25–30 kg m$^{-2}$) and obesity (BMI > 30 kg m$^{-2}$) is increasing [30].
2. Lack of activity may contribute to an increase in BMI and increased body weight.
3. A high BMI has been associated with:
   - a significant limitation in range of motion (ROM) [31]
   - increased arthropathic pain
   - increased risk of developing target joints [32]
   - increased risk of diabetes mellitus, atherosclerosis, and cardiovascular disease, which may further damage arthropathic joints.
4. Regular physical activity should be advised.
5. If functional limitations restrict daily activities, a physiotherapist familiar with hemophilia may be able to suggest appropriate alternatives.
6. In some cases, referral to a dietician may be indicated.

**Hypertension**
1. Hemophilia patients have a higher mean blood pressure, are twice as likely to have hypertension, and use more anti-hypertensive medication compared with the general population [33,34].
2. In view of increased risk of bleeding, hypertensive patients with hemophilia should be treated adequately and have their blood pressure checked regularly.
3. In the absence of other cardiovascular risk factors, a systolic blood pressure $\leq$ 140 mmHg and a diastolic pressure $\leq$ 90 mmHg should be maintained.

**Diabetes mellitus (DM)**
1. The prevalence of DM in hemophilia is not well documented, but was observed to be higher in a cohort of mild hemophilia [35].
2. In aging hemophilia patients, especially among those who are overweight, glucose levels should be checked annually.
3. If treatment with insulin is indicated, subcutaneous injections can be administered without bleeding complications. (Level 5) [24]

**Hypercholesterolemia**
1. Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population [36].
2. Cholesterol levels (total cholesterol, HDL, and LDL fraction) should be measured in aging hemophilia patients at risk of cardiovascular disease.
3. Treatment is indicated if cholesterol levels are high. As a general rule, the total cholesterol/HDL ratio should not be higher than 8.

**Cardiovascular disease**
1. Hemophilia patients appear to have a reduced risk of mortality from ischemic cardiovascular disease, but the number of deaths from this cause is increasing [34,37,38].
2. A possible association between the occurrence of myocardial infarction and previous administration of clotting factor concentrates has been described [39,40].
3. Hemophilia patients with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist [41,42].
4. For acute coronary syndromes requiring percutaneous cardiac intervention (PCI):
   - Adequate correction with clotting factor concentrates before PCI and until 48 h after PCI is required. (Level 4) [40,41,43]
   - High factor levels should be avoided to prevent occlusive thrombi. During complete correction:
     - Heparin can be administered according to standard cardiologic treatment protocols.
     - Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban) used in PCI with stenting can be administered.
   - Radial artery access site, if technically possible, is preferred over femoral, to minimize retroperitoneal or groin bleeds. (Level 4) [40,41,43]
   - Factor concentrates should be given for the duration of dual antiplatelet therapy, usually about 2 weeks, aiming at trough levels of 30 IU dL$^{-1}$ [41].
• Prolonged use of aspirin is not recommended in severe hemophilia. Its use in patients on regular intensive prophylaxis is possible, although the data available are inadequate [41].

**Psychosocial impact**

1. In the aging patient, the presence of crippling, painful arthropathy can affect quality of life and may lead to loss of independence [44].
2. Patients may be confronted with unexpected emotional problems due to memories of negative experiences related to hemophilia (such as hospitalization) during their youth.
3. Adaptations at home or at work and an adequate pain schedule are indicated to improve quality of life and preserve independence.
4. Active psychosocial support should be provided by a social worker, hemophilia nurse, physician and/or psychologist.

2.8 von Willebrand disease and rare bleeding disorders

1. The WFH is committed to providing support and information to patients, families, and clinicians on other hereditary bleeding disorders and many such patients are cared for in hemophilia treatment centers.
2. These guidelines are intended for the treatment of hemophilia. Recent publications that address the principles of diagnosis and treatment of von Willebrand disease (VWD) and rare bleeding disorders include:


**References**


Section 3. Laboratory diagnosis

1. A correct diagnosis is essential to ensure that a patient gets the appropriate treatment. Different bleeding disorders may have very similar symptoms.

2. Accurate diagnosis can only be made with the support of a comprehensive and accurate laboratory service. This is dependent on the laboratory following strict protocols and procedures, which require:
   - knowledge and expertise in coagulation laboratory testing
   - use of the correct equipment and reagents
   - quality assurance

3. For detailed information on technical aspects and specific instructions on screening tests and factor assays, please consult the WFH’s *Diagnosis of Hemophilia and Other Bleeding Disorders: A Laboratory Manual, Second edition* [1].

3.1 Knowledge and expertise in coagulation laboratory testing

Principles of diagnosis

1. Understanding the clinical features of hemophilia and the appropriateness of the clinical diagnosis.

2. Using screening tests to identify the potential cause of bleeding, for example, platelet count, bleeding time (BT; in select situations), or other platelet function screening tests, prothrombin time (PT), and activated partial thromboplastin time (APTT).

3. Confirmation of diagnosis by factor assays and other appropriate specific investigations.

Technical aspects

Preparation of the patient prior to taking a blood sample—

1. Fasting is not normally necessary before collection of blood for investigation of possible bleeding disorders, although a gross excess of lipids may affect some automated analyzers.

2. Patients should avoid medications that can affect test results such as aspirin, which can severely affect platelet function and prolong the bleeding/closure time.

3. Patients should avoid strenuous exercise immediately prior to venipuncture.

4. If a patient is particularly stressed by the sample collection procedure, the levels of FVIII and von Willebrand factor may be temporarily elevated.

Sample collection—

1. The sample should be collected as per standard guidelines [2].

2. The sample should preferably be collected near the laboratory to ensure quick transport.

3. Samples should be tested within 4 h of collection.

4. Results of tests can change according to the sample storage conditions. Higher temperatures (>25°C) lead to loss of FVIII activity over time, whereas sample storage in the cold (2–8°C) leads to cold activation. The sample should therefore be maintained at temperatures between 20°C and 25°C where possible, but for no more than 4 h.

5. Venipuncture must be clean and the sample collected within 1 min of tourniquet application without prolonged venous stasis.

6. Blood should be withdrawn into a plastic syringe or an evacuated collection system. The needle should be 19–21 gauge for adults and 22–23 gauge for small children. Collection through peripheral venous catheters or non-heparinized central venous catheters can be successful for many tests of hemostasis.

7. Blood from an indwelling catheter should be avoided for coagulation tests.

8. Frothing of the blood sample should also be avoided. It is often useful to discard the first 2 mL of blood collected.

9. The sample should be collected in citrate tubes containing 0.105 M–0.109 M (c3.2%) aqueous trisodium citrate dihydrate, maintaining the proportion of blood to citrate as 9:1. If the tube contains less than 80% of the target volume, results may be adversely affected. The higher strength concentration of 3.8% trisodium citrate is no longer recommended.

10. Prompt and adequate mixing with citrate solution should be done by gentle inversion.

11. If the sample cannot be processed within 4 h of collection, the platelet poor plasma can be frozen at −30°C and stored for a few weeks, or up to 6 months if stored at −70°C [3]. Storage at −20°C is usually inadequate.

12. Frozen samples must be thawed rapidly for 4–5 min at 37°C to avoid formation of cryoprecipitate.

Preparation of platelet-poor plasma (PPP)—

1. PPP should be prepared as per standard guidelines [2].

2. PPP is prepared by centrifugation of a sample at a minimum of 1700 g for at least 10 min at room temperature (i.e., not refrigerated).

3. PPP may be kept at room temperature (20°C–25°C) prior to testing.

4. Plasma that has been hemolyzed during collection and processing should not be analyzed.
End-point detection—

1. Many laboratories now have some form of semi or fully automated coagulation analyzers. Accurately detecting the clotting end-point using a manual technique requires considerable expertise, particularly if the clotting time is prolonged or if the fibrinogen concentration is low, and the clot is thin and wispy.

2. For manual testing, the tube should be tilted three times every five-seconds through an angle of approximately 90° during observation. The tube should be immersed in a water bath at 37°C between tilting.

Screening tests—

1. Platelet count, BT, PT, and APTT may be used to screen a patient suspected of having a bleeding disorder [4].

2. Bleeding time lacks sensitivity and specificity and is also prone to performance-related errors. Therefore other tests of platelet function such as platelet aggregometry are preferred when available [5,6].

3. Based on the results of these tests, the category of bleeding disorder may be partially characterized to guide subsequent analysis. (Table 3-1).

4. These screening tests may not detect abnormalities in patients with mild bleeding disorders including some defects of platelet function, FXIII deficiency, and those rare defects of fibrinolysis, which may be associated with a bleeding tendency.

Correction studies—

1. Correction or mixing studies using pooled normal plasma (PNP) will help define whether prolonged coagulation times are due to factor deficiency or circulating anticoagulants of inhibitors. Correction studies with FVIII/FIX-deficient plasma may be used to identify the particular deficiency if a factor assay is not available.

2. Phenotypic tests lack sensitivity and specificity for the detection of carriers. Some obligate carriers may have a normal FVIII:C/VWF:Ag ratio. Genotypic testing is a more precise method of carrier detection and is therefore recommended.

3. One-stage assays based on APTT are the most commonly used techniques. The following assay features are important:

   - FVIII- and FIX-deficient plasma must completely lack FVIII and FIX respectively, i.e., contain <1 IU dL⁻¹, and have normal levels of other clotting factors.
   - The reference/calibration plasma, whether commercial or locally prepared, must be calibrated in international units (i.e., against an appropriate WHO international standard).
   - At least three different dilutions of the reference plasma and the test sample under analysis are needed for a valid assay.
   - Use of a single dilution of test sample substantially reduces the precision of the test and may lead to completely inaccurate results in the presence of some inhibitors.
   - When assaying test samples from subjects with moderate or severe hemophilia, an extended or separate calibration curve may be needed. It is not acceptable to simply extend the calibration curve by extrapolation without analyzing additional dilutions of the calibration plasma.
   - Some cases of genetically confirmed mild hemophilia A have normal FVIII activity when the one-stage assay is used for diagnosis, but reduced activity in chromogenic and two-stage clotting assays. The reverse can also occur. This means that more than one type of FVIII assay

<table>
<thead>
<tr>
<th>Possible diagnosis</th>
<th>PT</th>
<th>APTT*</th>
<th>BT</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemophilia A or B**</td>
<td>Normal</td>
<td>Prolonged*</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>VWD</td>
<td>Normal</td>
<td>Normal or prolonged*</td>
<td>Normal or prolonged</td>
<td>Normal or reduced</td>
</tr>
<tr>
<td>Platelet defect</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or prolonged</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

*aResults of APTT measurements are highly dependent on the laboratory method used for analysis.

**The same pattern can occur in the presence of FXI, FXII, prekallikrein, or high molecular weight kininogen deficiencies.
Inhibitor testing—
1. The presence of some form of inhibitor is suspected when there is a prolonged APTT that is not fully corrected by mixing patient plasma with PNP.
2. The most frequently encountered functional inhibitors of hemostasis are lupus anticoagulants (LA), which are not directed against specific clotting factors and which should be excluded.
3. Results of APTT testing on mixtures of test and normal plasma can be difficult to interpret, particularly as in acquired hemophilia there may initially be a full correction of APTT in the presence of a potent specific anti-FVIII antibody.
4. Most FVIII inhibitors that occur secondary to replacement therapy in subjects with hemophilia A show a characteristic pattern: the APTTT of a patient/PNP mixture is intermediate, i.e., between the APTTs of the two materials, and is further prolonged when the mixture is incubated at 37°C for 1–2 h.
5. Confirmation that an inhibitor is directed against a specific clotting factor requires a specific inhibitor assay.
6. The Nijmegen modification of the FVIII inhibitor assay offers improved specificity and sensitivity over the original Bethesda assay. (Level 1) [9,10]
7. It is performed as follows:
   - Buffered PNP (providing FVIII) is mixed with test plasma and incubated at 37°C
   - After 2 h, the residual FVIII is measured by comparison against the FVIII in a control mixture comprised of buffered PNP and FVIII-deficient plasma, which has been incubated alongside the test mixture.
   - Residual FVIII is converted into inhibitor units using a semi-log plot of the residual FVIII against inhibitor convention, which has been constructed using the assumption that 100% residual = 0 BU mL⁻¹ inhibitor, and 50% residual = 1.0 BU mL⁻¹ (the latter being the internationally agreed convention for defining inhibitor activity).
   - When residual FVIII activity is <25%, the patient plasma must be retested after dilution to avoid underestimation of the inhibitor potency.
   - An inhibitor titer of ≥ 0.6 BU mL⁻¹ is to be taken as clinically significant [11].

Trained personnel—
1. Even the simplest coagulation screening tests are complex by nature.
2. A laboratory scientist/technologist with an interest in coagulation must have an in-depth understanding of the tests to achieve accurate results.
3. In some cases, it may be beneficial to have a laboratory scientist/technologist who has had further training in a specialist center.

3.2 Use of the correct equipment and reagents
1. Equipment and reagents are the tools of the trade of any laboratory. The following requirements are necessary for accurate laboratory testing.

Equipment
1. A 37°C ± 0.5°C water bath.
2. A good light source placed near the water bath to accurately observe clot formation.
3. Stopwatches.
4. Automated pipettes (either fixed or variable volume) capable of delivering 0.1 mL and 0.2 mL accurately and precisely.
5. Clean soda glass test tubes (7.5 cm × 1.2 cm) for clotting tests. Reuse of any glassware consumables should be avoided whenever possible, unless it can be demonstrated that test results are unaffected by the process used. Plasticware used in coagulation analyzers should not be re-used.
6. An increasingly large number of semi-automated and fully automated coagulometers are now available. In many cases, this equipment has the following advantages:
   - Accuracy of end-point reading.
   - Improved precision of test results.
   - Ability to perform multiple clot-based assays.
   - Reduction of observation errors (the end-point of the reaction is typically measured electromechanically or photoelectrically).
   - Use of polystyrene (clear) cuvettes instead of glass tubes.
7. All equipment requires maintenance to be kept in good working order.
   - When equipment is purchased, consideration should be given to, and resources put aside, for regular maintenance by a product specialist.
   - Pipettes should be checked for accurate sample/reagent delivery.
   - Water baths, refrigerators, and freezers should undergo regular temperature checks.
8. Good results can be obtained using basic equipment and technology provided that good laboratory practice is observed. These skills can then be adapted to more automated technology.
Selection of coagulometers—

1. Many coagulation analyzers are provided as a package of instrument and reagent, and both components can influence the results obtained. This needs to be taken into account when evaluating and selecting a system. Other important issues to consider are:
   - type of tests to be performed and the workload, as well as workflow, in the laboratory
   - operational requirements (power, space, humidity, temperature, etc.)
   - service requirements and breakdown response
   - throughput and test repertoire
   - costs
   - ability to combine with reagents from other manufacturers
   - user-programmable testing
   - comparability between results on primary analyzer and any back-up methods
   - compatibility with blood sample tubes and plasma storage containers in local use
   - safety assessment (mechanical, electrical, microbiological)
   - availability of suitable training

2. Information is required in relation to the performance characteristics of the system. This can be obtained from a variety of sources including the published literature and manufacturers’ data, but may also require some form of local assessment. Aspects to consider include:
   - precision of testing with a target of <3% of CV for screening tests and <5% for factor assays
   - carry-over
   - interfering substances
   - reagent stability on board analyzer
   - comparability with other methods
   - sample identification
   - data handling, software, and quality control
   - training required
   - reliability

3. A number of published guidelines and recommendations describe the evaluation of coagulation analyzers [12,13].

Reagents

1. It is good practice to ensure continuity of supply of a chosen reagent, with attention paid to continuity of batches and long shelf-life. This may be achieved by asking the supplier to batch hold for the laboratory, if possible.

2. Changing to a different source of material is not recommended unless there are supply problems or because of questionable results. Different brands may have completely different sensitivities and should not be run side by side.

3. Instructions supplied with the reagent should be followed.

4. Particular attention should be paid to reagent stability. Once a reagent is reconstituted or thawed for daily use, there is potential for deterioration over time depending on the conditions of storage and use.

5. Once an appropriate test and reagents have been decided upon, normal/reference ranges should ideally be defined, and must take account of the conditions used locally.

3.3 Quality assurance

1. Quality assurance (QA) is an umbrella term used to describe all measures taken to ensure the reliability of laboratory testing and reporting.

2. QA covers all aspects of the diagnosis process from sample-taking, separation and analysis, and internal quality control through to reporting of the result and ensuring that it reaches the clinician.

3. It is the responsibility of everyone involved to make sure that the procedures are followed in the correct manner.

Internal quality control (IQC)

1. IQC is used to establish whether a series of techniques and procedures are being performed consistently over a period of time.

2. IQC measures are taken to ensure that the results of laboratory investigations are reliable enough to assist clinical decision making, monitor therapy, and diagnose hemostatic abnormalities.

3. IQC is particularly useful to identify the degree of precision of a particular technique.

4. For screening tests of hemostasis, normal and abnormal plasma samples should be included regularly. At least one level of IQC sample should be included with all batches of tests.

External quality assessment (EQA)

1. Laboratories are strongly advised to participate in an external quality assessment scheme (EQAS) to audit the effectiveness of the IQC systems in place.

2. EQAS helps to identify the degree of agreement between the laboratory results and those obtained by other laboratories.

3. Participation in such a scheme helps build confidence between a laboratory and its users.

4. The WFH IEQAS is specifically designed to meet the needs of hemophilia treatment centers worldwide. The scheme includes analyses relevant to the diagnosis and management of bleeding. Details of this scheme, which is operated in conjunction with the U.K. National External Quality Assessment Service for Blood Coagulation in
Sheffield, U.K., can be obtained from the WFH [14].

5. Other national and international quality assessment schemes are also available.

6. For a laboratory to attain a high level of testing reliability and to participate successfully in EQAS, it must have access to appropriate reagents and techniques and an appropriate number of adequately trained staff.

References


8. Oldenburg J, Pavlova A. Discrepancy between one-stage and chromogenic FVIII activity assay results can lead to misdiagnosis of haemophilia A phenotype. Haemostaseologie 2010; 30: 207–11.


Section 4. Hemostatic agents

4.1 Clotting factor concentrates

1. The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or fresh frozen plasma for the treatment of hemophilia and other inherited bleeding disorders. (Level 5) [1,2]

2. The comprehensive WFH Guide for the Assessment of Clotting Factor Concentrates reviews factors affecting the quality, safety, licensing, and assessment of plasma-derived products and the important principles involved in selecting suitable products for the treatment of hemophilia [2].

3. The WFH also publishes and regularly updates a Registry of Clotting Factor Concentrates, which lists all currently available products and their manufacturing details [3].

4. The WFH does not express a preference for recombinant over plasma-derived concentrates and the choice between these classes of product must be made according to local criteria.

5. Currently manufactured plasma-derived concentrates produced to Good Manufacturing Practice (GMP) standards have an exemplary safety record with respect to lipid-coated viruses, such as HIV and HCV.

6. Product safety is the result of efforts in several areas:
   - improved donor selection (exclusion of at-risk donors)
   - improved screening tests of donations, including nucleic acid testing (NAT)
   - type and number of in-process viral inactivation and/or removal steps

7. The risk of prion-mediated disease through plasma-derived products exists. In the absence of a reliable screening test for variant Creutzfeldt-Jakob disease (vCJD), and with no established manufacturing steps to inactivate the vCJD prion, this problem is currently being handled by excluding plasma from all donors perceived to be at risk. As new information evolves in this field, constant awareness of current scientific recommendations is needed for those involved in making decisions regarding choice of clotting factor concentrate for people with hemophilia.

Product selection
When selecting plasma-derived concentrates, consideration needs to be given to both the plasma quality and the manufacturing process. Two issues deserve special consideration:

1. Purity of product
2. Viral inactivation/elimination

Purity—

1. Purity of concentrates refers to the percentage of the desired ingredient (e.g., FVIII), relative to other ingredients present.
2. There is no universally agreed classification of products based on purity.
3. Concentrates on the market vary widely in their purity.
4. Some products have high or very high purity at one stage of the production process, but are subsequently stabilized by albumin, which lowers their final purity. Generally speaking, products with higher purity tend to be associated with low manufacturing yields. These concentrates are, therefore, costlier.
5. Concentrates of lower purity may give rise to allergic reactions [4,5]. Patients who experience these repeatedly with a particular product may benefit from the administration of an antihistamine immediately prior to infusion or from use of a higher purity concentrate.
6. Plasma-derived FVIII concentrates may contain variable amounts of von Willebrand factor (VWF). It is therefore important to ascertain a product’s VWF content (as measured by ristocetin cofactor activity) if it is used for the treatment of VWD [6].

7. For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture. Products containing activated clotting factors may predispose to thromboembolism. (Level 2) [7,8]

8. The viral safety of products is not related to purity, as long as adequate viral elimination measures are in place.

Viral inactivation/elimination—

1. In-process viral inactivation is the single largest contributor to the safety of plasma-derived concentrates [9].
2. There is a growing tendency to incorporate two specific viral-reducing steps in the manufacturing process of concentrates.
   - Heat treatment is generally effective against a broad range of viruses, both with and without a lipid envelope, including HIV, HAV, HBV, and HCV.
• Solvent/detergent treatment is effective against HBV, HCV, and HIV, but does not inactivate non-enveloped viruses such as HAV.

3. Some viruses (such as human parvovirus B19) are relatively resistant to both types of process. None of the current methods can inactivate prions.

4. Nano (ultra) filtration can be used to remove small viruses such as parvovirus, but filtration techniques currently in use do not eliminate the risk of transmission [10].

5. A product created by a process that incorporates two viral reduction steps should not automatically be considered better than one that only has one specific viral inactivation step.

6. If only one step is used, this step should preferably inactivate viruses with and without lipid envelopes.

**FVIII concentrates**

1. FVIII concentrates are the treatment of choice for hemophilia A.

2. All plasma-derived products currently in the market are listed in the WFH Registry of Clotting Factor Concentrates [3]. Consult the product insert for specific details.

**Dosage/administration—**

1. Vials of factor concentrates are available in dosages ranging from approximately 250–3000 units each.

2. In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2 IU dL\(^{-1}\). (Level 4) [11]

3. The half-life of FVIII is approximately 8–12 h.

4. The patient’s factor level should be measured 15 min after the infusion to verify the calculated dose. (Level 4) [11]

5. The dose is calculated by multiplying the patient’s weight in kilograms by the factor level in IU dL\(^{-1}\) desired, multiplied by 0.5. **Example:** 50 kg × 40 (IU dL\(^{-1}\) level desired) × 0.5 = 1,000 units of FVIII. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement required based on type of hemorrhage.

6. FVIII should be infused by slow IV injection at a rate not to exceed 3 mL per min in adults and 100 units per min in young children, or as specified in the product information leaflet. (Level 5) [12]

7. Subsequent doses should ideally be based on the half-life of FVIII and on the recovery in an individual patient for a particular product.

8. It is best to use the entire vial of FVIII once reconstituted, although many products have been shown to have extended stability after reconstitution.

9. Continuous infusion avoids peaks and troughs and is considered by some to be advantageous and more convenient. However, patients must be monitored frequently for pump failure. (Level 3) [13,14]

10. Continuous infusion may lead to a reduction in the total quantity of clotting factor concentrates used and can be more cost-effective in patients with severe hemophilia [15]. However, this cost-effectiveness comparison can depend on the doses used for continuous and intermittent bolus infusions [16].

11. Dose for continuous infusion is adjusted based on frequent factor assays and calculation of clearance. As FVIII concentrates of very high purity are stable in IV solutions for at least 24–48 h at room temperature with less than 10% loss of potency, continuous infusion for a similar number of hours is possible.

**FIX concentrates**

1. FIX concentrates are the treatment of choice for hemophilia B.

2. All plasma-derived products currently in the market are listed in the WFH Registry of Clotting Factor Concentrates [3]. Consult the product information guide for specific details.

3. FIX concentrates fall into two classes:
   - Pure FIX concentrates, which may be plasma-derived or recombinant.
   - FIX concentrates that also contain factors II, VII, IX, and X, also known as prothrombin complex concentrates (PCCs), are only rarely used.

4. Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to PCC (Level 2) [7,8], particularly in the following instances:
   - Surgery
   - Liver disease
   - Prolonged therapy at high doses
   - Previous thrombosis or known thrombotic tendency
   - Concomitant use of drugs known to have thrombogenic potential, including antifibrinolytic agents

5. Pure FIX products are free of the risks of thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of PCCs.
Dosage/administration—

1. Vials of FIX concentrates are available in doses ranging from approximately 250–2000 units each.
2. In absence of an inhibitor, each unit of FIX per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1 IU dL\(^{-1}\). (Level 4) [11]
3. The half-life is approximately 18–24 h.
4. The patient’s FIX level should be measured approximately 15 min after infusion to verify calculated doses. (Level 4) [11]
5. Recombinant FIX (rFIX) has a lower recovery than plasma-derived products, such that each unit of FIX per kg body weight infused will raise the FIX activity by approximately 0.8 IU dL\(^{-1}\) in adults and 0.7 IU dL\(^{-1}\) in children under 15 years of age. The reason for the lower recovery of rFIX is not entirely clear [17].
6. To calculate dosage, multiply the patient’s weight in kilograms by the factor level desired. Example: 50 kg × 40 (IU dL\(^{-1}\) level desired) = 2000 units of plasma-derived FIX. For rFIX, the dosage will be 2000 ÷ 0.8 (or 2000 × 1.25) = 2500 units for adults, and 2000 ÷ 0.7 (or 2000 × 1.43) = 2860 units for children. Refer to Tables 7-1 and 7-2 for suggested factor level and duration of replacement therapy based on type of hemorrhage.
7. FIX concentrates should be infused by slow IV injection at a rate not to exceed a volume of 3 mL per min in adults and 100 units per min in young children, or as recommended in the product information leaflet. (Level 5) [12]
8. If used, PCCs should generally be infused at half this rate. Consult the product information leaflet for instructions. (Level 2) [18]
9. Purified FIX concentrates may also be administered by continuous infusion (as with FVIII concentrates).
10. Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors. In such patients, infusions may need to be covered with hydrocortisone [19]. Changing the brand of clotting factor concentrate sometimes reduces symptoms.

4.2 Other plasma products

1. The WFH supports the use of coagulation factor concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) due to concerns about their quality and safety. However, the WFH recognizes the reality that they are still widely used in countries around the world where it is the only available or affordable treatment option. (Level 5) [1,2]
2. Cryoprecipitate and FFP are not subjected to viral inactivation procedures (such as heat or solvent/ detergent treatment), leading to an increased risk of transmission of viral pathogens, which is significant with repeated infusions [1].
3. Certain steps can be taken to minimize the risk of transmission of viral pathogens. These include:
   - Quarantining plasma until the donor has been tested or even retested for antibodies to HIV, hepatitis C, and HBsAg – a practice that is difficult to implement in countries where the proportion of repeat donors is low.
   - Nucleic acid testing (NAT) to detect viruses – a technology that has a potentially much greater relevance for the production of cryoprecipitate than for factor concentrates, as the latter are subjected to viral inactivation steps [20].
4. Allergic reactions are more common following infusion of cryoprecipitate than concentrate [21].

Fresh frozen plasma (FFP)

1. As FFP contains all the coagulation factors, it is sometimes used to treat coagulation factor deficiencies.
2. Cryoprecipitate is preferable to FFP for the treatment of hemophilia A and VWD. (Level 4) [22]
3. Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable (Level 4) [23]. However, as FFP and cryo-poor plasma contain FIX, they can be used for the treatment of hemophilia B in countries unable to afford plasma-derived FIX concentrates.
4. It is possible to apply some forms of virucidal treatment to packs of FFP (including solvent/ detergent treatment) and the use of treated packs is recommended. However, virucidal treatment may have some impact on coagulation factors. The large scale preparation of pooled solvent/ detergent-treated plasma has also been shown to reduce the proportion of the largest multimers of VWF [24,25].

Dosage/administration—

1. One ml of fresh frozen plasma contains 1 unit of factor activity.
2. It is generally difficult to achieve FVIII levels higher than 30 IU dL\(^{-1}\) with FFP alone.
3. FIX levels above 25 IU dL\(^{-1}\) are difficult to achieve. An acceptable starting dose is 15–20 mL kg\(^{-1}\). (Level 4) [22]
Cryoprecipitate

1. Cryoprecipitate is prepared by slow thawing of fresh frozen plasma (FFP) at 4°C for 10–24 h. It appears as an insoluble precipitate and is separated by centrifugation.
2. Cryoprecipitate contains significant quantities of FVIII (about 3–5 IU mL⁻¹), VWF, fibrinogen, and FXIII, but not FIX or FXI. The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X, and XI.
3. Due to concerns about the safety and quality of cryoprecipitate, its use in the treatment of congenital bleeding disorders is not recommended and can only be justified in situations where clotting factor concentrates are not available. (Level 4) [1,22,26]
4. Although the manufacture of small pool, viral-inactivated cryoprecipitate has been described, it is uncertain whether it offers any advantage with respect to overall viral safety or cost benefit over conventionally manufactured large pool concentrates [27].

Dosage/administration—

1. A bag of cryoprecipitate made from one unit of FFP (200–250 mL) may contain 70–80 units of FVIII in a volume of 30–40 mL.

4.3 Other pharmacological options

In addition to conventional coagulation factor concentrates, other agents can be of great value in a significant proportion of cases. These include:

1. desmopressin
2. tranexamic acid
3. epsilon aminocaproic acid

Desmopressin (DDAVP)

1. Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analog of vasopressin that boosts plasma levels of FVIII and VWF [28].
2. DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using a clotting factor concentrate. (Level 3) [28,29]
3. Desmopressin does not affect FIX levels and is of no value in hemophilia B.
4. Each patient’s response should be tested prior to therapeutic use, as there are significant differences between individuals. The response to intranasal desmopressin is more variable and therefore less predictable. (Level 3) [28,29]
5. DDAVP is particularly useful in the treatment or prevention of bleeding in carriers of hemophilia. (Level 3) [30]
6. Although DDAVP is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the postpartum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF. (Level 3) [31,32]
7. Obvious advantages of DDAVP over plasma products are the much lower cost and the absence of any risk of transmission of viral infections.
8. DDAVP may also be useful to control bleeding and reduce the prolongation of bleeding time associated with disorders of hemostasis, including some congenital platelet disorders.
9. The decision to use DDAVP must be based on both the baseline concentration of FVIII, the increment achieved, and the duration of treatment required.

Dosage/administration—

1. Although desmopressin is given subcutaneously in most patients, it can also be administered by intravenous infusion or by nasal spray. It is important to choose the correct preparation of desmopressin because some lower dose preparations are used for other medical purposes.
2. Appropriate preparations include:
   - 4 µg mL⁻¹ for intravenous use
   - 15 µg mL⁻¹ for intravenous and subcutaneous use
   - 150 µg per metered dose as nasal spray
3. A single dose of 0.3 µg kg⁻¹ body weight, either by intravenous or subcutaneous route, can be expected to boost the level of FVIII three- to six-fold. (Level 4) [28,33]
4. For intravenous use, DDAVP is usually diluted in at least 50–100 mL of physiological saline and given by slow intravenous infusion over 20–30 min. The peak response is seen approximately 60 min after administration either intravenously or subcutaneously.
5. Closely spaced repetitive use of DDAVP over several days may result in decreased response (tachyphylaxis). Factor concentrates may be needed when higher factor levels are required for a prolonged period. (Level 3) [34]
6. Rapid infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
8. A single metered intranasal spray of 1.5 mg mL\(^{-1}\) in each nostril is appropriate for an adult. For an individual with a body weight of less than 40 kg, a single dose in one nostril is sufficient. (Level 4) [35,36]

9. Although the intranasal preparation is available, some patients find it difficult to use and it may be less efficacious than when given subcutaneously.

10. As a result of its antidiuretic activity, water retention and hyponatremia can be a problem. When repeated doses are given, the plasma osmolality or sodium concentration should be measured. (Level 4) [28,37]

11. In most adults, hyponatremia is uncommon.

12. Due to water retention, DDVAP should be used with caution in young children and is contraindicated in children under 2 years of age who are at particular risk of seizures secondary to cerebral edema due to water retention. (Level 4) [38,39]

13. There are case reports of thrombosis (including myocardial infarction) after infusion of DDAVP. It should be used with caution in patients with a history, or who are at risk, of cardiovascular disease. (Level 4) [33]

**Tranexamic acid**

1. Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin.

2. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders [40].

3. **Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia.** (Level 4) [40]

4. It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia). (Level 2) [41–43]

5. Tranexamic acid is particularly valuable in the setting of dental surgery and may be used to control oral bleeding associated with eruption or shedding of teeth. (Level 4) [42,44]

**Dosage/administration—**

1. Tranexamic acid is usually given as an oral tablet three to four times daily. It can also be given by intravenous infusion two to three times daily, and is also available as a mouthwash.

2. Gastrointestinal upset (nausea, vomiting, or diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. When administered intravenously, it must be infused slowly as rapid injection may result in dizziness and hypotension.

3. A syrup formulation is also available for pediatric use. If this is not available, a tablet can be crushed and dissolved in clean water for topical use on bleeding mucosal lesions.

4. Tranexamic acid is commonly prescribed for 7 days following dental extractions to prevent postoperative bleeding.

5. Tranexamic acid is excreted by the kidneys and the dose must be reduced if there is renal impairment to avoid toxic accumulation.

6. The use of tranexamic acid is contraindicated for the treatment of hematuria as its use may prevent dissolution of clots in the ureters, leading to serious obstructive uropathy and potential permanent loss of renal function.

7. Similarly, the drug is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.

8. Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates. (Level 4) [45]

9. Tranexamic acid should **not** be given to patients with FIX deficiency receiving prothrombin complex concentrates, as this will exacerbate the risk of thromboembolism. (Level 5) [46]

10. If treatment with both agents is deemed necessary, it is recommended that at least 12 h elapse between the last dose of APCC and the administration of tranexamic acid. (Level 5) [46]

11. In contrast, thromboembolism is less likely when tranexamic acid is used in combination with rFVIIa to enhance hemostasis. (Level 4) [47]

**Epsilon aminocaproic acid**

1. Epsilon aminocaproic acid (EACA) is similar to tranexamic acid, but is less widely used as it has a shorter plasma half-life, is less potent, and is more toxic [40].

**Dosage/administration—**

1. EACA is typically administered to adults orally or intravenously every 4–6 h up to a maximum of 24 g day\(^{-1}\) in an adult.

2. A 250 mg mL\(^{-1}\) syrup formulation is also available.

3. Gastrointestinal upset is a common complication; reducing the dose often helps.

4. Myopathy is a rare adverse reaction specifically reported in association with aminocaproic acid therapy (but not tranexamic acid), typically occurring after administration of high doses for several weeks.

5. The myopathy is often painful and associated with elevated levels of creatine kinase and even myoglobinuria.

6. Full resolution may be expected once drug treatment is stopped.
GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA e29

References


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Section 5. Treatment of specific hemorrhages

1. Bleeding in patients with hemophilia can occur at different sites (Tables 1-2 and 1-3), each of which requires specific management.

2. As a general principle in case of large internal hemorrhage, hemoglobin should be checked and corrected while other measures are being planned. Measures of hemodynamic stability, such as pulse and blood pressure, should be monitored as indicated.

5.1 Joint hemorrhage (hemarthrosis)

1. A joint bleed is defined as an episode characterized by rapid loss of range of motion as compared with baseline that is associated with any combination of the following: pain or an unusual sensation in the joint, palpable swelling and warmth of the skin over the joint [1].

2. The onset of bleeding in joints is frequently described by patients as a tingling sensation and tightness within the joint. This “aura” precedes the appearance of clinical signs.

3. The earliest clinical signs of a joint bleed are increased warmth over the area and discomfort with movement, particularly at the ends of range.

4. Later symptoms and signs include pain at rest, swelling, tenderness, and extreme loss of motion.

5. A re-bleed is defined as worsening of the condition either on treatment or within 72 h after stopping treatment [1].

6. A target joint is a joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period.

7. Following a joint bleed, flexion is usually the most comfortable position, and any attempt to change this position causes more pain.

8. Secondary muscle spasm follows as the patient tries to prevent motion and the joint appears “frozen”.

9. The goal of treatment of acute hemarthrosis is to stop the bleeding as soon as possible. This should ideally occur as soon as the patient recognizes the “aura”, rather than after the onset of overt swelling and pain.

10. Evaluate the patient clinically. Usually, X-rays and ultrasounds are not indicated.

11. Administer the appropriate dose of factor concentrate to raise the patient’s factor level suitably (refer to Tables 7-1 and 7-2). (Level 2) [2-5]

12. The definitions listed in Table 5-1 are recommended for the assessment of response to treatment of an acute hemarthrosis. [1]

13. Instruct the patient to avoid weight-bearing, apply compression, and elevate the affected joint. (Level 3) [4]

14. Consider immobilizing the joint with a splint until pain resolves.

15. Ice/cold packs may be applied around the joint for 10-15 min every 2-4 h for pain relief, if found beneficial. Do not apply ice in direct contact with skin. [39]

16. If bleeding does not stop, a second infusion may be required. If so, repeat half the initial loading dose in 12 h (hemophilia A) or 24 h (hemophilia B). (Level 3) [4]

17. Further evaluation is necessary if the patient’s symptoms continue longer than 3 days. The presence of inhibitors, septic arthritis, or fracture should be considered if symptoms and findings persist.

18. Rehabilitation must be stressed as an active part of the management of acute joint bleeding episodes. (Level 2) [4,6,7]

- As soon as the pain and swelling begin to subside, the patient should be encouraged to change the position of the affected joint from a position of comfort to a position of function, gradually decreasing the flexion of the joint and striving for complete extension.

- This should be done as much as possible with active muscle contractions. Gentle passive assistance may be used initially and with caution if muscle inhibition is present.

- Early active muscle control must be encouraged to minimize muscle atrophy and prevent chronic loss of joint motion.

- Active exercises and proprioceptive training must be continued until complete prebleed

Table 5-1. Definition of response to treatment of acute hemarthrosis [1].

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Complete pain relief within 8 hours and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy within 72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Significant pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but requiring more than one dose of replacement therapy within 72 hours for complete resolution</td>
</tr>
<tr>
<td>Moderate</td>
<td>Modest pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection and requiring more than one injection within 72 hours but without complete resolution</td>
</tr>
<tr>
<td>None</td>
<td>None or minimal improvement, or condition worsens, within approximately 8 h after the initial injection.</td>
</tr>
</tbody>
</table>

The above definitions of response to treatment of an acute hemarthrosis relate to inhibitor negative individuals with hemophilia. These definitions may require modification for inhibitor positive patients receiving bypassing agents as hemostatic cover or patients who receive factor concentrates with extended half-lives.
joint range of motion and functioning are restored and signs of acute synovitis have dissipated [8].

- If exercises are progressed judiciously, factor replacement is not necessarily required before exercising.

**Arthrocentesis**

1. **Arthrocentesis** (removal of blood from a joint) may be considered in the following situations:
   - a bleeding, tense, and painful joint, which shows no improvement 24 h after conservative treatment
   - joint pain that cannot be alleviated
   - evidence of neurovascular compromise of the limb
   - unusual increase in local or systemic temperature and other evidence of infection (septic arthritis) (Level 3) [4,9,10]

2. Inhibitors should be considered as a reason for persistent bleeding despite adequate factor replacement. The presence of inhibitors must be ruled out before arthrocentesis is attempted.

3. The early removal of blood should theoretically reduce its damaging effects on the articular cartilage [10]. If there is a large accumulation of blood, it will also decrease pain.

4. Arthrocentesis is best performed soon after a bleed under strictly aseptic conditions.

5. When necessary, arthrocentesis should be performed under factor levels of at least 30–50 IU dL\(^{-1}\) for 48–72 h. Arthrocentesis should not be performed in circumstances where such factor replacement is not available. In the presence of inhibitors, other appropriate hemostatic agents should be used for the procedure, as needed. (Level 3) [4]

6. A large bore needle, at least 16-gauge, should be used.

7. The joint should be immobilized with mild compression.

8. Weight-bearing should be avoided for 24–48 h.

9. Physiotherapy should be initiated as described above.

5.2 **Muscle hemorrhage**

1. Muscle bleeds can occur in any muscle of the body, usually from a direct blow or a sudden stretch.

2. A muscle bleed is defined as an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and functional impairment e.g., a limp associated with a calf bleed [1].

3. Early identification and proper management of muscle bleeds are important to prevent permanent contracture, re-bleeding, and formation of pseudotumors.

4. Sites of muscle bleeding that are associated with neurovascular compromise, such as the deep flexor muscle groups of the limbs, require immediate management to prevent permanent damage and loss of function. These groups include:
   - the iliopsoas muscle (risk of femorocutaneous, crural, and femoral nerve palsy)
   - the superior-posterior and deep posterior compartments of the lower leg (risk of posterior tibial and deep peroneal nerve injury)
   - the flexor group of forearm muscles (risk of Volkmann’s ischemic contracture)

5. Bleeding can also occur in more superficial muscles such as the biceps brachii, hamstrings (triceps surae), gastrocnemius, quadriceps, and the gluteal muscles.

6. Symptoms of muscle bleeds are:
   - aching in the muscle
   - maintenance of the limb in a position of comfort
   - severe pain if the muscle is stretched
   - pain if the muscle is made to actively contract
   - tension and tenderness upon palpation and possible swelling

7. Raise the patient’s factor level as soon as possible, ideally when the patient recognizes the first signs of discomfort or after trauma. If there is neurovascular compromise, maintain the levels for 5–7 days or longer, as symptoms indicate (refer to Tables 7-1 and 7-2). (Level 3) [11–13]

8. Rest the injured part and elevate the limb.

9. Splint the muscle in a position of comfort and adjust to a position of function as pain allows.

10. Ice/cold packs may be applied around the muscle for 15–20 min every four to 6 h for pain relief if found beneficial. Do not apply ice in direct contact with skin.

11. Repeat infusions are often required for 2–3 days or much longer in case of bleeds at critical sites causing compartment syndromes and if extensive rehabilitation is required. (Level 5) [14,15]

12. The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases. (Level 5) [16,17]

13. Hemoglobin level should be checked and corrected if needed as muscle bleeds can result in significant blood loss.

14. Physiotherapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function. (Level 4) [12,18]

15. Factor coverage during this process is prudent, unless the physiotherapist is experienced with hemophilia management. Serial casting or splint-
ing may be required. Supportive bracing will be required if there has been nerve damage.

16. Increasing pain during physical therapy can suggest re-bleeding and should be regularly evaluated [19].

**Iliopsoas hemorrhage**

1. This type of muscle hemorrhage has a unique presentation. Signs may include pain in the lower abdomen, groin, and/or lower back and pain on extension, but not on rotation, of the hip joint. There may be paresthesia in the medial aspect of the thigh or other signs of femoral nerve compression such as loss of patellar reflex and quadriceps weakness. The symptoms may mimic acute appendicitis, including a positive Blumberg's sign.

2. Immediately raise the patient's factor level. Maintain the levels for 5–7 days or longer, as symptoms indicate (refer to Tables 7-1 and 7-2). (Level 4) [20–22]

3. Hospitalize the patient for observation and control of pain. Maintain strict bed rest. Ambulation with crutches is not permitted, as ambulation requires contraction of the muscle. (Level 4) [20–22]

4. It is useful to confirm the diagnosis and monitor recovery with an imaging study (ultrasonography, CT scan, or MRI). (Level 4) [20–22]

5. Limit the patient's activity until pain resolves and hip extension improves. A carefully supervised program of physiotherapy is key to restoring full activity and function and preventing re-bleeding. Restoration of complete hip extension before returning to full activity is recommended. (Level 4) [20–22]

6. If residual neuromuscular deficits persist, further orthotic support may be necessary.

**5.3 Central nervous system hemorrhage/head trauma**

1. This is a medical emergency. Treat first before evaluating.

2. All posttraumatic head injuries, confirmed or suspected, and significant headaches must be treated as intracranial bleeds. Sudden severe pain in the back may be associated with bleeding around the spinal cord. Do not wait for further symptoms to develop or for laboratory or radiologic evaluation.

3. Immediately raise the patient’s factor level when significant trauma or early symptoms occur. Further doses will depend on imaging results. Maintain factor level until etiology is defined. If a bleed is confirmed, maintain the appropriate factor level for 10–14 days (refer to Tables 7-1 and 7-2). (Level 4) [23,24]

4. Intracranial hemorrhage may be an indication for prolonged secondary prophylaxis (3–6 months), especially where a relatively high risk of recurrence has been observed (e.g., in the presence of HIV infection). (Level 3) [23,25,26]

5. Immediate medical evaluation and hospitalization are required. A CT scan or MRI of the brain should be performed. Neurological consultation should be sought early. (Level 4) [27,28]

6. Severe headache may also be a manifestation of meningitis in immunocompromised patients.

**5.4 Throat and neck hemorrhage**

1. This is a medical emergency because it can lead to airway obstruction. Treat first before evaluating.

2. Immediately raise the patient’s factor level when significant trauma or symptoms occur. Maintain the factor levels until symptoms resolve (refer to Tables 7-1 and 7-2). (Level 4) [15,29,30]

3. Hospitalization and evaluation by a specialist are essential. (Level 5) [15]

4. To prevent hemorrhage in patients with severe tonsillitis, treatment with factor may be indicated, in addition to bacterial culture and treatment with appropriate antibiotics.

**5.5 Acute gastrointestinal (GI) hemorrhage**

1. Immediately raise the patient’s factor levels. Maintain the factor level until hemorrhage has stopped and etiology is defined (refer to Tables 7-1 and 7-2). (Level 4) [31,32]

2. Acute gastrointestinal hemorrhage may present as hematemesis, hematochezia, or melena.

3. For signs of GI bleeding and/or acute hemorrhage in the abdomen, medical evaluation and possibly hospitalization are required.

4. Hemoglobin levels should be regularly monitored. Treat anemia or shock, as needed.

5. Treat origin of hemorrhage as indicated.

6. EACA or tranexamic acid may be used as adjunctive therapy for patients with FVIII deficiency and those with FIX deficiency who are not being treated with prothrombin complex concentrates.

**5.6 Acute abdominal hemorrhage**

1. An acute abdominal, including retroperitoneal, hemorrhage can present with abdominal pain and distension and can be mistaken for a number of infectious or surgical conditions. It may also present as a paralytic ileus. Appropriate radiologic studies may be necessary.
2. **Immediately** raise the patient’s factor levels. Maintain the factor levels (refer to Tables 7-1 and 7-2) until the etiology can be defined, then treat appropriately in consultation with a specialist. (Level 4) [15,29,30]

5.7 **Ophthalmic hemorrhage**

1. This is uncommon unless associated with trauma or infection.
2. **Immediately** raise the patient’s factor level. Maintain the factor level as indicated (refer to Tables 7-1 and 7-2). (Level 4) [15,29,30]
3. Have the patient evaluated by an ophthalmologist as soon as possible.

5.8 **Renal hemorrhage**

1. Treat painless hematuria with complete bed rest and vigorous hydration (3 L m$^{-2}$ body surface area) for 48 h. Avoid DDAVP when hydrating intensively. (Level 4) [33]
2. Raise the patient’s factor levels (refer to Tables 7-1 and 7-2) if there is pain or persistent gross hematuria and watch for clots and urinary obstruction. (Level 4) [33,34]
3. Do not use antifibrinolytic agents. (Level 4) [33]
4. Evaluation by an urologist is essential for evaluation of a local cause if hematuria (gross or microscopic) persists or if there are repeated episodes.

5.9 **Oral hemorrhage**

1. Early consultation with a dentist or oral and maxillofacial surgeon is essential to determine the source of bleeding. The most common causes are:
   - dental extraction
   - gingival bleeding often due to poor oral hygiene
   - trauma
2. Local treatments must be considered treat the hemorrhage. These may include:
   - direct pressure on the area using a damp gauze swab, maintained for at least 15 min
   - sutures to close the wound
   - application of local hemostatic agents
   - antibiotics, especially in gingival bleeding due to poor oral hygiene
   - use of EACA or tranexamic acid as a mouthwash
3. An appropriate dose of regular paracetamol/acetaminophen will help control the pain.
4. Antifibrinolytic agents should not be used systematically in patients with FIX deficiency that are being treated with large doses of prothrombin complex concentrates or in patients with inhibitors being treated with activated prothrombin complex concentrates (APCC). (Level 4) [35,36]
5. Factor replacement may be required as directed by the hemophilia center.
6. Oral EACA or tranexamic acid should be used if appropriate. (Level 4) [37,38]
7. Advise the patient to avoid swallowing blood.
8. Advise the patient to avoid using mouthwashes until the day after the bleeding has stopped.
9. Advise the patient to eat a soft diet for a few days.
10. Evaluate and treat for anemia as indicated.

5.10 **Epistaxis**

1. Place the patient’s head in a forward position to avoid swallowing blood and ask him to gently blow out weak clots. Firm pressure with gauze soaked in ice water should be applied to the anterior softer part of the nose for 10–20 min.
2. Factor replacement therapy is often not necessary unless bleeding is severe or recurrent [15,29].
3. Antihistamines and decongestant drugs are useful for bleeds specifically related to allergies, upper respiratory infections, or seasonal changes.
4. If bleeding is prolonged or occurs frequently, evaluate for anemia and treat appropriately.
5. EACA or tranexamic acid applied locally in a soaked gauze is helpful.
6. Consult with an otolaryngologist if the bleed is persistent or recurrent. Anterior or posterior nasal packing may be needed to control bleeding.
7. Epistaxis can often be prevented by increasing the humidity of the environment, applying gels (e.g., petroleum jelly or saline drops/gel) to the nasal mucosa to preserve moisture, or administering saline spray.

5.11 **Soft tissue hemorrhage**

1. Symptoms will depend on the site of hemorrhage.
2. Factor replacement therapy is not necessary for most superficial soft tissue bleeding. The application of firm pressure and ice may be helpful [15,29].
3. Evaluate the patient for severity of hemorrhage and possible muscular or neurovascular involvement. Rule out possible trauma to spaces containing vital organs, such as the head or abdomen.
4. Open compartmental hemorrhage, such as in the retroperitoneal space, scrotum, buttocks, or thighs, can result in extensive blood loss. Treat with factor immediately if this situation is suspected.
5. Hemoglobin levels and vital signs should be regularly monitored.

5.12 Lacerations and abrasions
1. Treat superficial lacerations by cleaning the wound, then applying pressure and steri-strips.

2. For deep lacerations, raise the factor level (refer to Tables 7-1 and 7-2), and then suture. (Level 4) [15,29,30]
3. Sutures may be removed under cover of factor concentrate.

References
1 Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. JTH 2012 (in press).
Section 6. Complications of hemophilia

6.1 Musculoskeletal complications

1. The most common sites of bleeding are the joints and muscles of the extremities.
2. Depending on the severity of the disease, bleeding episodes may be frequent and without apparent cause (see Table 1-1).
3. In the child with severe hemophilia, the first hemarthrosis typically occurs when the child begins to crawl and walk: usually before 2 years of age, but occasionally later.
4. If inadequately treated, repeated bleeding will lead to progressive deterioration of the joints and muscles, severe loss of function due to loss of motion, muscle atrophy, pain, joint deformity, and contractures within the first one to two decades of life [1,2].

Synovitis

1. Following acute hemarthrosis, the synovium becomes inflamed, is hyperemic and extremely friable.
2. Failure to manage acute synovitis can result in repeated hemarthroses [1,2].
3. During this stage, the joint requires protection with a removal splint or compressive bandaging.
4. Activities should be restricted until swelling and temperature of the joint return to baseline.
5. In some cases, COX-2 inhibitors may be useful.
6. Range of motion is preserved in the early stages. Differentiation between hemarthrosis and synovitis is made by performing a detailed physical examination of the joint.
7. The presence of synovial hypertrophy may be confirmed by ultrasonography or MRI. Plain radiographs and particularly MRI will assist in defining the extent of osteochondral changes.
8. With repeated bleeding, the synovium becomes chronically inflamed and hypertrophied, and the joint appears swollen (this swelling is usually not tense, nor is it particularly painful): this is chronic synovitis.
9. As the swelling continues to increase, articular damage, muscle atrophy, and loss of motion will progress to chronic hemophilic arthropathy.
10. The goal of treatment is to deactivate the synovium as quickly as possible and preserve joint function (Level 5) [3,4]. Options include:
    - factor concentrate replacement, ideally given with the frequency and at dose levels sufficient to prevent recurrent bleeding (Level 2) [5–8]
        • If concentrates are available in sufficient doses, short treatment courses (6–8 weeks) of secondary prophylaxis with intensive physiotherapy are beneficial.
    - physiotherapy (Level 2) [9,10], including:
        • daily exercise to improve muscle strength and maintain joint motion
        • modalities to reduce secondary inflammation, if available [11]
        • functional training [12]
    - a course of NSAIDs (COX-2 inhibitors), which may reduce inflammation (Level 2) [13,14]
    - functional bracing, which allows the joint to move but limits movement at the ends of range where the synovium can be pinched and which may prevent new bleeding. [15]
    - synovectomy

Synovectomy—

1. Synovectomy should be considered if chronic synovitis persists with frequent recurrent bleeding not controlled by other means. Options for synovectomy include chemical or radioisotopic synoviorthesis, and arthroscopic or open surgical synovectomy. (Level 4) [16,17]
2. Non-surgical synovectomy is the procedure of choice.
3. Radioisotopic synovectomy using a pure beta emitter (phosphorus-32 or yttrium-90) is highly effective, has few side effects, and can be accomplished in an outpatient setting. (Level 4) [18,19]
    - A single dose of clotting factor is often sufficient for a single injection of the isotope.
    - Rehabilitation is less intense than after surgical synovectomy, but is still required to help the patient regain strength, proprioception, and normal functional use of the joint.
4. If a radioisotope is not available, chemical synoviorthesis with either rifampicin or oxytetracycline chlorhydrate is an appropriate alternative [20,21].
    - Chemical synoviorthesis involves weekly injections until the synovitis is controlled.
    - These painful injections require the administration of intra-articular xilocaine a few minutes before injection of the sclerosing agent, oral analgesics (a combination of acetaminophen/paracetamol and an opioid), and a dose of clotting factor concentrate prior to each injection.
    - The low cost of the chemical agent is offset by the need for multiple injections of factor concentrate.
    - Rehabilitation, as described for radioactive synovectomy, is recommended.
5. Surgical synovectomy, whether open or arthroscopic, requires a large supply of clotting factor for both surgery and the lengthy period of reha-
bilitation. The procedure must be performed by an experienced team at a dedicated hemophilia treatment center. It is only considered when other less invasive and equally effective procedures fail.

Chronic hemophilic arthropathy

1. Chronic hemophilic arthropathy can develop any time from the second decade of life (and sometimes earlier), depending on the severity of bleeding and its treatment.

2. The process is set in motion by the immediate effects of blood on the articular cartilage during hemarthrosis [1,2] and reinforced by persistent chronic synovitis and recurrent hemarthroses, resulting in irreversible damage.

3. With advancing cartilage loss, a progressive arthritic condition develops that includes:
   - secondary soft tissue contractures
   - muscle atrophy
   - angular deformities

4. Deformity can also be enhanced by contracture following muscle bleeds or neuropathy.

5. Loss of motion is common, with flexion contractures causing the most significant functional loss.

6. Joint motion and weight bearing can be extremely painful.

7. As the joint deteriorates, swelling subsides due to progressive fibrosis of the synovium and the capsule.

8. If the joint becomes ankylosed, pain may diminish or disappear.

9. The radiographic features of chronic hemophilic arthropathy depend on the stage of involvement.
   - Radiographs will only show late osteochondral changes. [22,23]
   - Ultrasound or MRI examination will show early soft tissue and osteochondral changes. [24–26]
   - Cartilage space narrowing will vary from minimal to complete loss.
   - Bony erosions and subchondral bone cysts will develop, causing collapse of articular surfaces that can lead to angular deformities.
   - Fibrous/bony ankylosis may be present. [27]

10. The goals of treatment are to improve joint function, relieve pain, and assist the patient to continue/resume normal activities of daily living.

11. Treatment options for chronic hemophilic arthropathy depend on:
   - the stage of the condition
   - the patient’s symptoms
   - the impact on the patient’s lifestyle and functional abilities
   - the resources available

12. Pain should be controlled with appropriate analgesics. Certain COX-2 inhibitors may be used to relieve arthritic pain (see ‘Pain Management’). (Level 2) [13,14]

13. Supervised physiotherapy aiming to preserve muscle strength and functional ability is a very important part of management at this stage. Secondary prophylaxis may be necessary if recurrent bleeding occurs as a result of physiotherapy. (Level 2) [9,10]

14. Other conservative management techniques include:
   - serial casting to assist in correcting deformities. [28,29]
   - bracing and orthotics to support painful and unstable joints. [15]
   - walking aids or mobility aids to decrease stress on weight-bearing joints.
   - adaptations to the home, school, or work environment to allow participation in community activities and employment and to facilitate activities of daily living. [30]

15. If these conservative measures fail to provide satisfactory relief of pain and improved functioning, surgical intervention may be considered. Surgical procedures, depending on the specific condition needing correction, may include:
   - extra-articular soft tissue release to treat contractures.
   - arthroscopy to release intra-articular adhesions and correct impingement. [31]
   - osteotomy to correct angular deformity.
   - prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder, elbow). [32]
   - elbow synovectomy with radial head excision. [33]
   - arthrodesis of the ankle, which provides excellent pain relief and correction of deformity with marked improvement in function. Recent improvements in ankle replacement surgery may pose an alternative for persons with hemophilia in the future. [34,35].

16. Adequate resources, including sufficient factor concentrates and postoperative rehabilitation, must be available to proceed with any surgical procedure. (Level 3) [36–38]

Principles of physiotherapy/physical medicine in hemophilia

1. Physiotherapists and occupational therapists and/or physiatrists should be part of the core hemophilia team. Their involvement with patients and their families should begin at the time of diagno-
sis, and they remain important to the patient throughout their lifespan.

2. Their role in the management of the patient with hemophilia includes the following [9,39–41]:
   - **Assessment**
     - Determining the site of an acute bleed
     - Regular assessment throughout life
     - Preoperative assessment
   - **Education**
     - Of the patient and family regarding musculoskeletal complications and their treatment
     - Of school personnel regarding suitable activities for the child, immediate care in case of a bleed, and modifications in activities that may be needed after bleeds.
   - **Treatment of acute bleeds**, chronic synovitis, and chronic arthropathy using a variety of techniques including hydrotherapy, heat, ice, electrical nerve stimulation, pulsed diathermy, ultrasound as well as various orthoses for pain relief and restoration of function.

**Pseudotumors**

1. The pseudotumor is a potentially limb and life-threatening condition unique to hemophilia that occurs as a result of inadequately treated soft tissue bleeds, usually in muscle adjacent to bone, which can be secondarily involved. It is most commonly seen in a long bone or the pelvis.

2. If not treated, the pseudotumor can reach enormous size, causing pressure on the adjacent neurovascular structures and pathologic fractures. A fistula can develop through the overlying skin.

3. Diagnosis is made by the physical finding of a localized mass.

4. Radiographic findings include a soft tissue mass with adjacent bone destruction.

5. A more detailed and accurate evaluation of a pseudotumor can be obtained with CT scan and MRI.

6. Management depends on the site, size, rate of growth, and effect on adjoining structures. Options include factor replacement and monitoring, aspiration, and surgical ablation.
   - A 6-week course of treatment with factor is recommended, followed by repeat MRI. If the tumor is decreasing, continue with factor and repeat MRI for three cycles. (Level 4) [42,43]
   - Proceed to surgery if necessary, which will be much easier if the tumor has shrunk.
   - Aspiration of the pseudotumor followed by injections of fibrin glue, arterial embolization, or radiotherapy may heal some lesions. Surgery may be needed for others. (Level 4) [44,45]
   - Surgical excisions, including limb amputations, may be necessary for large pseudotumors, particularly if they erode long bones. Large abdominal pseudotumors present a special challenge in surgical management of hemophilia; surgery must only be performed by teams with experience in hemophilia.

**Fractures**

1. Fractures are not frequent in people with hemophilia, possibly due to lower levels of ambulation and intensity of activities [46]. However, a person with hemophilic arthropathy may be at risk for fractures around joints that have significant loss of motion and in bones that are osteoporotic.

2. Treatment of a fracture requires immediate factor concentrate replacement. (Level 4) [46–48]

3. Clotting factor levels should be raised to at least 50% and maintained for 3–5 days. (Level 4) [3,46–48]

4. Lower levels may be maintained for 10–14 days while the fracture becomes stabilized and to prevent soft tissue bleeding.

5. The management plan should be appropriate for the specific fracture, including operative treatment under appropriate coverage of clotting factor concentrates.

6. Circumferential plaster should be avoided; splints are preferred. (Level 4) [46]

7. Compound/infected fractures may require external fixators. [49]

8. Prolonged immobilization, which can lead to significant limitation of range of movement in the adjacent joints, should be avoided. (Level 4) [46,47]

9. Physiotherapy should be started as soon as the fracture is stabilized to restore range of motion, muscle strength, and function. [39]

**Principles of orthopedic surgery in hemophilia**

For important considerations related to performing surgical procedures in persons with hemophilia, please see “Surgery and Invasive Procedures”. Specific issues in relation to orthopedic surgery include:

1. Orthopedic surgeons should have had specific training in surgical management of persons with hemophilia. [3]

2. Performing multiple site elective surgery in a simultaneous or staggered fashion to use clotting factor concentrates judiciously should be considered. (Level 3) [50]
3. Local coagulation enhancers may be used. Fibrin glue is useful to control oozing when operating in extensive surgical fields. (Level 3) [36,51,52]

4. Postoperative care in patients with hemophilia requires closer monitoring of pain and often higher doses of analgesics in the immediate postoperative period. (Level 5) [36]

5. Good communication with the postoperative rehabilitation team is essential [39]. Knowledge of the details of the surgery performed and intraoperative joint status will facilitate planning of an appropriate rehabilitation program.

6. Postoperative rehabilitation should be carried out by a physiotherapist experienced in hemophilia management.

7. Rehabilitation may have to progress more slowly in persons with hemophilia.

8. Adequate pain control is essential to allow appropriate exercise and mobilization.

9. These principles also apply to fixation of fractures and excision of pseudotumors.

6.2 Inhibitors

1. “Inhibitors” in hemophilia refer to IgG antibodies that neutralize clotting factors.

2. In the current era in which clotting factor concentrates have been subjected to appropriate viral inactivation, inhibitors to FVIII or FIX are considered the most severe treatment-related complication in hemophilia.

3. The presence of a new inhibitor should be suspected in any patient who fails to respond clinically to clotting factors, particularly if he has been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished.

4. Inhibitors are more frequently encountered in persons with severe hemophilia compared with those with moderate or mild hemophilia.

5. The cumulative incidence (i.e., lifetime risk) of inhibitor development in severe hemophilia A is in the range of 20–30% and approximately 5–10% in moderate or mild disease. [53,54]

6. In severe hemophilia A, the median age of inhibitor development is 3 years or less in developed countries. In moderate/mild hemophilia A, it is is closer to 30 years of age, and is often seen in conjunction with intensive FVIII exposure with surgery. [35,56]

7. In severe hemophilia, inhibitors do not change the site, frequency, or severity of bleeding. In moderate or mild hemophilia, the inhibitor may neutralize endogenously synthesized FVIII, thereby effectively converting the patient’s phenotype to severe.

8. Bleeding manifestations in moderate/mild hemophilia complicated by an inhibitor are more frequently reminiscent of those seen in patients with acquired hemophilia A (due to auto-antibodies to FVIII), with a greater predominance of mucocutaneous, urogenital, and gastrointestinal bleeding sites [57]. Consequently, the risk of severe complications or even death from bleeding may be significant in these patients.

9. Inhibitors are much less frequently encountered in hemophilia B, occurring in less than 5% of affected individuals. [58]

10. In all cases, inhibitors render treatment with replacement factor concentrates difficult. Patients on clotting factor therapy should therefore be screened for inhibitor development.

11. Confirmation of the presence of an inhibitor and quantification of the titer is performed in the laboratory, preferably using the Nijmegen-modified Bethesda assay (see ‘Inhibitor testing’). (Level 1) [59,60]

12. For children, inhibitors should be screened once every 5 exposure days until 20 exposure days, every 10 exposure days between 21 and 50 exposure days, and at least two times a year until 150 exposure days. (Level 5) [61]

13. For adults with more than 150 exposure days, apart from a 6–12 monthly review, any failure to respond to adequate factor concentrate replacement therapy in a previously responsive patient is an indication to assess for an inhibitor. (Level 3) [56,62–64]

14. Inhibitor measurement should also be done in all patients who have been intensively treated for more than 5 days, within 4 weeks of the last infusion. (Level 4) [63,65]

15. Inhibitors should also be assessed prior to surgery or if recovery assays are not as expected, and when clinical response to treatment of bleeding is sub-optimal in the postoperative period. (Level 2) [53,63,66]

16. A low responding inhibitor is defined as an inhibitor level that is persistently <5 BU mL−1, whereas a high responding inhibitor is defined by a level ≥5 BU mL−1.

17. High responding inhibitors tend to be persistent. If not treated for a long period, titer levels may fall or even become undetectable, but there will be a recurrent anamnestic response in 3–5 days when challenged again with specific factor products.

18. Some low titer inhibitors may be transient, disappearing within 6 months of initial documentation, despite recent antigenic challenge with factor concentrate.

19. Very low titer inhibitors may not be detected by the Bethesda inhibitor assay, but by a poor
recovery and/or shortened half-life (T-1/2) following clotting factor infusions.

Management of bleeding

1. Management of bleeding in patients with inhibitors must be in consultation with a center experienced in their management. (Level 5) [63,67]
2. Choice of treatment product should be based on titer of inhibitor, records of clinical response to product, and site and nature of bleed. (Level 4) [63,68]
3. Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding. (Level 4) [63,68]
4. Patients with a history of a high responding inhibitor but with low titers may be treated similarly in an emergency until an anamnestic response occurs, usually in 3–5 days, precluding further treatment with concentrates that only contain the missing factor. (Level 4) [63,68]
5. Porcine factor VIII prepared from the plasma of pigs has been effective in halting bleeding in some patients. The plasma-derived preparation is being superseded by a recombinant porcine factor VIII concentrate currently in clinical trials.
6. With an inhibitor level $\geq 5$ BU, the likelihood is low that specific factor replacement will be effective in overwhelming the inhibitor without ultra high dose continuous infusion therapy.
7. Alternative agents include bypassing agents such as recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates (PCC), including the activated forms (APCC).
8. The efficacy of two doses of rFVIIa and one dose of APCC for management of joint bleeding has been shown to be essentially equivalent. (Level 2) [69]
9. Notably, however, some patients respond better to one agent than the other, highlighting the need to individualize therapy. (Level 2) [69,70]
10. An anamnestic immune response should be expected in patients with hemophilia B and a FIX inhibitor treated with prothrombin complex concentrates—whether activated or not—since these concentrates all contain FIX.
11. On the other hand, the risk of anamnesis in patients with hemophilia A and an inhibitor treated with a(n) (activated) prothrombin complex concentrate will vary depending on the concentrate and its content of FVIII, which is generally minimal. It is estimated that APCC leads to an anamnestic response in approximately 30% of FVIII inhibitor patients.
12. Although there has been interest in the use of immunsuppressive therapies in patients with inhibitors, their role is not yet defined, and there is no consensus as to whether they have a place in the management of these patients.

Allergic reactions in patients with hemophilia B

1. Up to 50% of hemophilia B patients with inhibitors may have severe allergic reactions, including anaphylaxis, to FIX administration. Such reactions can be the first symptom of inhibitor development.
2. Newly diagnosed hemophilia B patients, particularly those with a family history and/or with genetic defects predisposed to inhibitor development, should be treated in a clinic or hospital setting capable of treating severe allergic reactions during the initial 10–20 treatments with FIX concentrates. Reactions can occur later, but may be less severe. (Level 4) [71,72]

Immune tolerance induction

1. In patients with severe hemophilia A, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy. (Level 2) [73,74]
2. Before ITI therapy, high-responding patients should avoid FVIII products to allow inhibitor titers to fall and to avoid persistent anamnestic rise. As noted, some patients may develop an anamnestic response to the inactive FVIII molecules in APCC as well. (Level 2) [75]
3. Optimal regimen (product or dose) for ITI remains to be defined. An international trial comparing 50 IU kg$^{-1}$ three times a week to 200 IU kg$^{-1}$ daily was recently stopped due to safety concerns (higher number of intercurrent bleeds) in the low-dose arm pending detailed analysis and interpretation of the data. [76]
4. Response to ITI may be less favorable in patients with moderate/mild hemophilia. [63]
5. Experience with ITI for hemophilia B inhibitor patients is limited. The principles of treatment in these patients are similar, but the success rate is much lower, especially in persons whose inhibitor is associated with an allergic diathesis.
6. Hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome during ITI, which is not always reversible upon cessation of ITI therapy. Alternative treatment schedules, including immunsuppressive therapies, are reported to be successful. [77]
Patients switching to new concentrates

1. For the vast majority of patients, switching products does not lead to inhibitor development.
2. However in rare instances, inhibitors in previously treated patients have occurred with the introduction of new FVIII concentrates.
3. In those patients, the inhibitor usually disappears after withdrawal of the new product.
4. Patients switching to a new factor concentrate should be monitored for inhibitor development. (Level 2) [53]

6.3 Transfusion-transmitted and other infection-related complications

1. The emergence and transmission of HIV, HBV and HCV through clotting factor products resulted in high mortality of people with hemophilia in the 1980s and early 1990s. [78,79]
2. Many studies conducted all over the world indicate that HIV, HBV, and HCV transmission through factor concentrate has been almost completely eliminated. [80,81]
3. This is a result of the implementation of several risk-mitigating steps, which include careful selection of donors and screening of plasma, effective virucidal steps in the manufacturing process, and advances in sensitive diagnostic technologies for detection of various pathogens. [82]
4. Recombinant factor concentrates have been adopted over the past two decades, particularly in developed countries. Recombinant products have contributed significantly to infection risk reduction.
5. The new challenge remains emerging and re-emerging infections, many of which are not amenable to current risk reduction measures. These include the non-lipid enveloped viruses and prions, for which diagnosis and elimination methods are still a challenge. [81,83,84]
6. As new treatments are continually emerging in this rapidly changing field, transfusion-transmitted infections in people with hemophilia are best managed by a specialist.

Principles of management of HIV infection in hemophilia

1. Knowledge and expertise in the treatment of HIV-infected people with hemophilia are currently limited to case series and reports. HIV treatment in people with hemophilia is therefore largely informed by guidelines used in the non-hemophilic population.
2. As part of the hemovigilance program, all people with hemophilia treated with plasma-derived products that are not adequately virus-inactivated should be tested for HIV at least every 6–12 months and whenever clinically indicated. (Level 4) [85]
3. The diagnosis, counseling, initiation of treatment, and monitoring of HIV, as well as the treatment of HIV-associated complications in infected people with hemophilia, should be the same as in the non-hemophilic population. (Level 2) [86,87]
4. None of the currently available classes of anti-HIV drugs are contraindicated in people with hemophilia. (Level 5) [88–90]

Principles of management of HCV infection in hemophilia

1. Assessment of HCV in people with hemophilia should include:
   • anti-HCV serology to determine exposure
   • HCV polymerase chain reaction (PCR) in those who are anti-HCV positive
   • HCV genotyping in those who are HCV PCR positive
   • liver function tests and non-invasive assessment of fibrosis and liver architecture
2. The current standard of treatment for HCV is pegylated interferon (PEG-INF) and ribavirin, which give sustained virological response in 61% of people with hemophilia. (Level 1) [91–96]
3. New antiviral therapies, in combination with these drugs, may improve sustained virologic response rates. [97]
4. HCV genotype 1 and HIV coinfection predict poorer response to anti-HCV therapy.
5. Where HCV eradication cannot be achieved, regular monitoring (every 6–12 months) for end-stage liver complication is recommended. (Level 3) [98]

Principles of management of HBV infection in hemophilia

1. All people with hemophilia treated with plasma-derived products that are not adequately virus-inactivated should be screened for hepatitis B antigen and anti-hepatitis B at least every 6–12 months and whenever clinically indicated. (Level 4) [99]
2. Active HBV infection should be managed as per local infectious disease guidelines and protocols.
3. Those without HBV immunity should be given the anti-HBV vaccine. Protective seroconversion should be rechecked following vaccination. (Level 4) [99–101]
4. People with hemophilia who do not seroconvert should be revaccinated with double the hepatitis B vaccine dose. (Level 4) [99,102]

Principles of management of bacterial infection in hemophilia

1. The risk factors for bacterial infections in people with hemophilia are venous access catheter insertion, surgical arthroplasty, and other surgical interventions. [103–105]

2. In general, joint aspiration to treat hemorrhoma should be avoided, unless done early under appropriate cover of factor replacement and with strict aseptic precautions to prevent infection. [106,107]

3. Bleeding is likely to delay healing and worsen infection and should therefore be well controlled. [108]

4. Control of the source of infection is of paramount importance in people with hemophilia. [109,110]

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Recht M, Pollmann H, Tagliaferri A et al. A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B. Haemophilia 2011; 17: 494–9.


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Section 7. Plasma factor level and duration of administration

7.1 Choice of factor replacement therapy protocols

1. The correlation shown between possible factor replacement therapy protocols and overall outcome in Fig. 7-1 depicts the choices that one needs to make when selecting doses and regimen of clotting factor concentrates.

2. While enabling a completely normal life should remain the ultimate goal of factor replacement therapy, this cannot be achieved immediately in people with hemophilia in all situations.

3. The availability of treatment products varies significantly around the world and there will therefore always be a range of doses with which people with hemophilia are treated. Lower doses may increase as the global availability of treatment products improves incrementally over time.

4. Tables 7-1 and 7-2 present commonly followed guidelines on plasma factor peak levels and duration of replacement that reflect the different practices in countries where there is no significant resource constraint (Table 7-1) and countries where treatment products are limited (Table 7-2).

5. With the lower doses for treating musculoskeletal bleeds listed in Table 7-2, it may only be possible to avoid major target joints and crippling deformities.

6. Higher doses listed in Table 7-1 have been shown to avoid joint damage, but the optimal dose needed to achieve this remains to be defined.

7. Observational studies documenting the musculoskeletal outcome of doses and protocols of factor replacement are extremely important in defining these issues.

8. Doses for prophylactic replacement of factor concentrates vary between different countries and also among centers in the same country.

9. Commonly used dosage for prophylactic factor replacement is 25–40 IU kg$^{-1}$ 2–3 times weekly in countries with less resource constraints (see Section 1 for details) [1–3].

10. In situations where there are greater constraints on supply of factor concentrates, prophylaxis may be initiated with lower doses of 10–20 IU kg$^{-1}$ 2–3 times per week. (Level 2) [4,5]

Fig. 7-1. Strategies for clotting factor replacement at different ages and impact on outcomes.
Table 7-1. Suggested plasma factor peak level and duration of administration (when there is no significant resource constraint) [6].

<table>
<thead>
<tr>
<th>Type of hemorrhage</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desired level (IU dL⁻¹)</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>Joint</td>
<td>40–60</td>
<td>1–2, may be longer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if response is inadequate</td>
</tr>
<tr>
<td>Superficial muscle/no NV compromise (except iliopsoas)</td>
<td>40–60</td>
<td>2–3, sometimes longer if response is inadequate</td>
</tr>
<tr>
<td>Iliopsoas and deep muscle with NV injury, or substantial blood loss</td>
<td>Initial</td>
<td>80–100</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>30–60</td>
</tr>
<tr>
<td>CNS/head</td>
<td>Initial</td>
<td>80–100</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>50</td>
</tr>
<tr>
<td>Throat and neck</td>
<td>Initial</td>
<td>80–100</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Initial</td>
<td>80–100</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>50</td>
</tr>
<tr>
<td>Renal</td>
<td>Initial</td>
<td>60–80</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>50</td>
</tr>
<tr>
<td>Deep laceration</td>
<td>Initial</td>
<td>50–80</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>50–80</td>
</tr>
<tr>
<td>Surgery (major)</td>
<td>Pre-op</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
<td>30–80</td>
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</tbody>
</table>

NV, neurovascular.

Table 7-2. Suggested plasma factor peak level and duration of administration (when there is significant resource constraint).

<table>
<thead>
<tr>
<th>Type of hemorrhage</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
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<td></td>
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<td>Throat and neck</td>
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NV, neurovascular.

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References


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Disclaimer

The World Federation of Hemophilia does not endorse particular treatment products or manufacturers; any reference to a product name is not an endorsement by the WFH. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side-effects recognized. These guidelines are intended to help develop basic standards of care for the management of hemophilia and do not replace the advice of a medical advisor and/or product insert information. Any treatment must be designed according to the needs of the individual and the resources available.

Disclosures

Dr. Srivastava has received grant support from the Bayer Hemophilia Awards Program and also serves on their Grants Review and Awards Committee. Dr. Key has acted as a paid consultant to Novo Nordisk and has received grant funding from Baxter. Dr. Kitchen has acted as a paid consultant to Novo Nordisk, Pfizer, and Bayer. Dr. Llinas has lectured for Baxter, Novo Nordisk, Pfizer, and Bayer and has performed clinical trials for Bayer and Baxter. Dr. Ludlam has received an educational grant from Novo Nordisk, has acted as medical advisor for Ipen, a consultant for Bojgen Idec and Baxter as well as Bayer, from which he has also received funding to attend medical conferences. Dr. Mauser-Bunschoten has received unrestricted research funding from CSL Behring, is a speaker for Bayer, Sanguin Bloedvoorziening, and Novo Nordisk, and has received funding for post-marketing surveillance by Wyeth and Baxter. Dr. Poon has attended advisory board meetings of CSL Behring, Novo Nordisk, Octapharma, and Pfizer. He has attended sponsored meetings on behalf of Baxter and Bayer, is a speaker for Pfizer, and acted as chair of Novo Nordisk’s expert panel on Glanzmann’s Thrombasthenia registry. The other authors have no competing interests to declare.
## Appendix I. Oxford Centre for Evidence-Based Medicine 2011 Levels Of Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross-sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross-sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or “poor or non-independent reference standard**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>


*Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

**As always, a systematic review is generally better than an individual study.
The diagnosis and management of von Willebrand disease: a
United Kingdom Haemophilia Centre Doctors Organization
guideline approved by the British Committee for Standards in
Haematology

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Keywords: diagnosis, management, guideline, United Kingdom Haemophilia Centre Doctors Organization, von Willebrand.

The guideline group was selected to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications in English from 2002 using the key word Willebrand. The writing group produced the draft guideline, which was subsequently reviewed by the A United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) advisory committee, a British Committee for Standards in Haematology (BCSH) sounding board of approximately 50 UK haematologists, and the BCSH executive; comments were incorporated where appropriate. The ‘GRADE’ system was used to quote levels and grades of evidence, details of which can be found in at http://www.bcshe-guidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_ GRADES_OF_RECOMMENDATION/43_GRADE.html. The objective of this guideline is to provide healthcare professionals with clear guidance on the diagnosis and management of patients with von Willebrand disease.

Guideline update

This is a single guideline replacing two separate guidelines on diagnosis and management respectively, published in 2004 (Laffan et al, 2004; Pasi et al, 2004). Where there has been no significant change in understanding or practice, the reader is referred to the earlier guidelines.

Major changes since last guideline

The principal changes have been increased understanding of the genetic basis of von Willebrand disease, a relaxation of definition and a focus on how laboratory tests can guide management.

What is von Willebrand disease?

Von Willebrand factor (VWF) is a large and complex plasma glycoprotein that is essential for normal haemostasis. It is well recognized that deficiency of VWF results in a bleeding disorder that varies in severity according to the degree of deficiency and the specific characteristics of the molecule and which may have features of both primary and secondary haemostatic defects. The complex structure of the protein and the wide range of plasma levels encountered in the population make laboratory assessment and diagnosis a challenging proposition. Since the last guidelines by this group (Laffan et al, 2004; Pasi et al, 2004), there have been considerable advances in understanding the genetics, function and clinical correlates of VWF, which have been incorporated into this revised and unified document. Here we define von Willebrand disease (VWD) as a bleeding disorder that is predominantly attributable to reduced levels of VWF activity. We recognize that this is frequently, but not always, attributable to a defect in the VWF gene (VWF). Our emphasis remains on practical guidance rather than taxonomic purity.

When patients present with mucocutaneous bleeding symptoms suggestive of a primary haemostatic disorder, a quantitative or qualitative abnormality of VWF is a possible cause or contributory factor. During the initial assessment it is important to remember that bleeding histories can be subjective and the disease characteristics can take time to
evolve; there is also overlap between symptoms suffered by people with VWD and the normal population (Sadler, 2003; Tosetto et al, 2013). Figure 1 shows the bleeding symptoms in an international study of type 1 VWD patients in comparison with unaffected family members (Tosetto et al, 2006). To improve decisions regarding the significance of bleeding symptoms, attempts have been made to develop a standardized bleeding assessment tool (BAT), with the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH/SSC) BAT being the most recent iteration (Rodeghiero et al, 2010; Rydz & James, 2012). These tools can help predict the likelihood of a bleeding disorder being present and have good negative predictive value but studies evaluating their ability to predict future bleeding episodes are lacking (Tosetto et al, 2013).

The plasma level of VWF in normal individuals varies over a six-fold range, from 0·40 to 2·40 iu/ml (Abildgaard et al, 1980), and VWF levels are approximately 25% lower in blood group O individuals than in non-O (Gill et al, 1987). A VWF activity <0·30 iu/ml is usually associated with bleeding symptoms and is more likely to be associated with a mutation in VWF, however these associations are less strong for VWF levels between 0·30 and 0·50 iu/ml (Eikenboom et al, 2006; James et al, 2006). In patients recruited to the MCMDM-1 VWD study, VWF antigen (VWF:Ag) or VWF ristocetin cofactor activity (VWF:RCo) values below 0·40 iu/ml significantly increased the likelihood of type 1 VWD (Tosetto et al, 2006). Amongst 117 obligate carriers of type 3 VWD (type 3 OC) with VWF <0·5 iu/ml, only 26% had bleeding symptoms (Sadler, 2003) and a more recent study (Castaman et al, 2006) did not demonstrate an independent correlation between bleeding score and VWF:Ag in 70 type 3 OC. These patients are also likely to have a normal physiological rise in VWF in response to stress. Therefore, mildly reduced VWF activity in isolation may be insufficient to result in significant bleeding. Nonetheless, some patients with only mildly reduced VWF levels do have significant bleeding symptoms: this is likely to reflect interaction with additional abnormalities in the haemostatic pathway, including mild platelet defects (Millar et al, 2008a; Daly et al, 2009).

A study of 280 patients with hereditary mucocutaneous bleeding found abnormalities of VWF and/or platelets in approximately one-third, whilst the majority had no identifiable laboratory abnormality. (Quiroga et al, 2007). Therefore, while identification of laboratory abnormalities may guide management, the primary diagnosis remains ‘abnormal bleeding’; for which risk factors may or may not be identified. Because VWF levels are relatively easy to measure (in comparison to platelet function) VWD has often been diagnosed in patients with bleeding symptoms and VWF levels that are only slightly reduced (0·3–0·5 iu/ml), giving the potentially misleading impression that this is the sole responsible factor.

A Bayesian approach to diagnosis of VWD combining laboratory data, personal bleeding history and family data has been evaluated: however an area of uncertainty remained (Tosetto et al, 2008). Thus, caution should be exercised in diagnosing VWD in patients with borderline VWF levels in the range 0·3–0·5 iu/ml in order to avoid the burden of an unnecessary diagnosis and the hazard of failing to complete further necessary investigations.

**Recommendations**

- **We recommend against the use of reference ranges or blood group-specific ranges for the diagnosis of von Willebrand disease (VWD) (2C).**
  - When investigating a patient with mucocutaneous bleeding a diagnosis of VWD can be made when von Willebrand factor (VWF) activity is <0·30 iu/ml (1B).
  - Patients with an appropriate bleeding history and VWF activity 0·3–0·5 iu/ml should be regarded as having primary haemostatic bleeding with reduced VWF as a risk factor rather than VWD. We suggest referring to this as ‘Low VWF’ (2C).
- **We recommend use of a bleeding score (e.g. Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis bleeding assessment tool) to standardize history taking (2C).**
  - When reviewing patients and families with an historical diagnosis of VWD, we suggest confirming the accuracy of that diagnosis (2A).
  - The incidental finding of VWF activity <0·30 iu/ml should be taken to indicate VWD or acquired von Willebrand syndrome (AVWS).

**Classification of VWD**

The simplified classification of VWD proposed by the ISTH (Sadler, 1994) is still in common use. Despite the potential for reclassification based on molecular defects, there has been
a reluctance to move to a more complex taxonomy; only minor qualifications were introduced when last reviewed (Sadler et al, 2006). Table I summarizes how the classification is currently applied.

In contrast to type 1 VWD, type 2 variants are usually linked to VWF and usually have a predictable laboratory and clinical phenotype. Misclassification remains an issue, typically between type 1 and type 2M (Nitu-Whalley et al, 2000). In the MCMDM-1 VWD study a third of the families recruited with an historical diagnosis of type 1 VWD had minor multimer abnormalities and a proportion of these were subsequently classified as type 2 VWD (Goodeve et al, 2007; Budde et al, 2008). However the relevance of subtle abnormalities in VWF multimer patterns remains controversial and they lack clear clinical significance (Budde et al, 2008; Castaman et al, 2008; James & Lillicrap, 2012).

Classification remains an artificial exercise and although it is of great use for study and research, it does not completely define or predict response to therapy and also has a variable relationship to genetics. From a clinical perspective, any further reclassification of VWD subtypes should focus on clinical utility and, ideally, correlate with responses to therapy.

Tests used for the primary diagnosis of VWD

von Willebrand disease cannot be excluded by a normal activated partial thromboplastin time (APTT). Although the overall sensitivity of the Platelet Function Analyser (PFA) for detecting VWD is reported to be 90%, it is close to 100% in type 2 (excluding 2N) and type 3 VWD but lower in type 1 VWD and may be normal when VWF activity is 0.3–0.5 iu/ml. Factor VIII (FVIII), VWF:Ag and measurements of VWF activity are the initial laboratory tests required to make a diagnosis of VWD and must be performed if VWD is suspected. A diagnostic algorithm is shown in Fig 2. Factors that can affect VWF levels (such as anxiety and needle phobia, the combined contraceptive pill, pregnancy and strenuous exercise) were discussed fully in our previous guideline (Laffan et al, 2004). Misdiagnosis can be minimized by ensuring at least two concordant sets of results are obtained. Samples should not be put on ice (Bohm et al, 2006).

Factor VIII assay

Factor VIII is measured using an APTT-based one stage clotting assay or chromogenic assay. Although FVIII half-life is regulated by VWF and is frequently reduced in VWD, FVIII levels may be normal in VWD.

Von Willebrand factor antigen

Plasma VWF:Ag levels are measured by immunological methods, usually by enzyme-linked immunosorbent assay

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Comments</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of VWF</td>
<td>Includes VWF mutations causing rapid VWF clearance (e.g. VWF Vicenza) and requires function:antigen ratio &gt; 0.6</td>
<td>Mostly autosomal dominant inheritance when VWF &lt; 0.3 iu/ml. Mutations of VWF in kindred with levels &gt; 0.3 iu/ml show variable penetrance</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative VWF defects</td>
<td>Some controversy exists regarding classification of VWF mutations associated with subtle reductions in HMW multimers</td>
<td>Mostly autosomal dominant</td>
</tr>
<tr>
<td>2A</td>
<td>Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers</td>
<td>Should be distinguished from PT-VWD, using either platelet agglutination tests or genetic testing. Cases with normal VWF multimer and platelet count have been described</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>2B</td>
<td>Increased affinity for platelet GPIb</td>
<td>This also includes defects of VWF collagen binding. May be combined quantitative/ qualitative defect</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased VWF-dependent platelet adhesion without selective deficiency of HMW multimers</td>
<td>Reduced VWF:FVIII binding defects are more commonly identified in a compound heterozygote state with a VWF null allele rather than the classical homozygous form</td>
<td></td>
</tr>
<tr>
<td>2N</td>
<td>Markedly decreased binding affinity for FVIII</td>
<td>Should be distinguished from mild haemophilia A</td>
<td>Autosomal recessive, frequent null VWF alleles. Bleeding symptoms in 26–48% of obligate carriers</td>
</tr>
<tr>
<td>3</td>
<td>Virtually complete deficiency of VWF</td>
<td>Equivalent to &lt; 0.03 iu/ml in most assays</td>
<td>Autosomal recessive, frequent null VWF alleles. Bleeding symptoms in 26–48% of obligate carriers</td>
</tr>
</tbody>
</table>

VWD, von Willebrand disease; PT-VWD, platelet type pseudo-VWD; VWF, von Willebrand factor; VWF, VWF gene; FVII, factor VIIIGPIb, glycoprotein Ib; HMW, high molecular weight.
(ELISA) or by automated immunoturbidimetric methods relying on latex particle agglutination. The latter may give falsely high results in the presence of rheumatoid factor.

**Von Willebrand factor activity**

Assessment of the ability of VWF to bind FVIII is discussed below. Here we examine the ability of VWF to support platelet adhesion by binding to platelet glycoprotein Ib (GPIb) and collagen.

**Binding of VWF to platelet GPIb.** Binding of VWF to platelet GPIb has traditionally been assessed by ristocetin cofactor activity (VWF:RCo). Ristocetin dimers bind to VWF and induce a conformational change facilitating VWF binding to platelet GPIb and thus cross-linking of platelets. Putative ristocetin binding sites flank the A1 domain, which contains the GPIb binding region. In the traditional assay the agglutination of normal fixed platelets is measured in dilutions of test plasma containing an excess of ristocetin and the patient’s VWF:RCo is determined by reference to a plasma standard. The agglutination is dependent on the presence of high molecular weight (HMW) multimers and an intact GPIb binding site.

The platelet agglutination method has been automated, with improvement in sensitivity and reproducibility (Lawrie et al, 2011). Other approaches to automation have used a monoclonal antibody to link recombinant GPIb to latex beads (Lawrie et al, 2011, 2013) or magnetic particles (Cabrera et al, 2013). The use of a recombinant GPIb with gain-of-function mutations can remove the requirement for ristocetin (Flood et al, 2011; Lawrie et al, 2013).

It must be recognized that using ristocetin rather than shear to induce VWF binding to GPIb is unphysiological. Thus sequence variations affecting the ristocetin binding sites on VWF can result in low VWF:RCo estimation in the absence of a physiological defect of VWF (Flood et al, 2009, 2010).

Assays based on monoclonal antibodies directed against the VWF GPIb-binding site, sometimes called ‘VWF activity assays’ have previously failed to detect type 2 VWD (Preston, 1998) and although more recent versions have improved precision and sensitivity, they are not yet sufficiently reliable to replace VWF:RCo (Chen et al, 2011; Favaloro et al, 2012). Pending further data we recommend they are not relied on for diagnosis.

**Binding of VWF to collagen (collagen binding activity, VWF:CB).** The primary collagen binding site of VWF is in the A3 domain.
domain. ELISAs are available to measure binding of patient VWF to immobilized collagen. VWF:CB is dependent on the presence of HMW multimers and an intact collagen binding site: assays using type III and type I/III mixtures of collagen have been found to give the best sensitivity to these factors (Favaloro, 2000). Although VWF:RCo and VWF:CB assess different aspects of VWF function, both are sensitive to the loss of HMW multimers and both the VWF:RCo to VWF:Ag ratio and the VWF:CB to VWF:Ag ratio will be reduced in type 2A disease, though the latter ratio is better at differentiating type 2A from type 1 disease (Favaloro et al., 2000).

Recommendaons

• In the initial investigation for VWD, FVIII, VWF:Ag and VWF activity should be measured(1A).
• VWF activity should be assessed by its ability to bind both GPIb and collagen (2B).
• We recommend against using assays based on monoclonal antibodies directed against the VWF GPIb-binding site (1B).

Secondary classification of VWD

Types 2A and 2M are qualitative disorders in which VWF function is significantly more reduced than VWF:Ag. Consequently, the VWF:RCo/VWF:Ag and the VWF:CB/VWF:Ag ratios are critically important in their differentiation from type 1. In the MCMDM-1 VWD study the median VWF:RCo/VWF:Ag ratio for 1166 healthy controls was 1.00 with a range of 0.59–1.62 (2.5th–97.5th centiles) (Goodeve et al., 2007). In a comparison of collagen-binding assays in 232 healthy controls, the lower limit of normal for VWF:CB/VWF:Ag was >0.76 for all types of collagen (Flood et al., 2012) and >0.6 for VWF:RCo/VWF:Ag. Thus patients with a function:antigen ratio <0.6 should be considered to have type 2 VWD and further tests should be performed for classification.

Multimer analysis

Plasma VWF multimer distribution can be analysed using non-reducing sodium dodecyl sulphate agarose gel electrophoresis. Following electrophoresis, a number of different methodologies have been described for VWF multimer visualization (Krizek & Rick, 2000; Ott et al., 2010; Pruthi et al., 2010). The gel agarose concentration can be modified in order to examine either the presence of HMW VWF multimers (c. 1%) or abnormalities of VWF satellite bands (1.5–3%).

Von Willebrand factor multimer analysis should not be performed until a diagnosis of VWD has been established. Multimer analysis is essential for the strict classification of type 2 VWD, but if not available, similar information can be cautiously inferred from the VWF:CB/VWF:Ag ratio (Favaloro, 2007).

Ristocetin-induced platelet agglutination (RIPA)

In normal individuals, low concentrations of ristocetin are not sufficient to initiate VWF-dependent platelet agglutination. Platelet agglutination at low ristocetin concentrations (<0.5–0.7 mg/ml) suggests a pathological enhancement of the VWF – GPIb interaction, which is characteristic of type 2B VWD and platelet-type pseudo-VWD (PT). Type 2B comprises a wide spectrum of severity overlapping with normality and in some patients the only abnormal feature present is RIPA positivity. If it is not practical to perform RIPA on all cases then it should always be performed when the VWF:RCo/VWF:Ag or VWF:CB/VWF:Ag ratio is reduced or if thrombocytopenia is present, bearing in mind that this may miss some mild forms of type 2B VWD (Federici et al., 2009).

VWF-FVIII binding assay (VWF:FVIII B)

Mutations of the FVIII binding site within the D’ and D3 domains of VWF can impair FVIII binding. If present in the homozygous state or in trans with a null allele this gives rise to type 2N VWD in which plasma VWF:Ag, VWF:RCo and VWF:CB are often normal but FVIII coagulant (FVIII:C) levels are markedly reduced. These mutations may also complicate a type 1 phenotype causing a disproportionate reduction in FVIII level. The ability of patient VWF to bind added exogenous normal FVIII can be assessed using an immuno-sorbent plate-binding assay (Zhukov et al., 2009) but these assays are technically difficult and genetic analysis provides a practical alternative.

Making a diagnosis in neonates and children

The diagnosis of VWD in neonates and infants is complicated by pre-analytical variation due to the difficulty in obtaining an unactivated and uncontaminated venous or cord sample and the prolonged physiological increase of VWF following delivery. In a study of full term normal infants the mean VWF level was 1.53 iu/ml at day 1 of life, reducing to 1.07 iu/ml at day 180 (Andrew et al., 1987). Thus the diagnosis of VWD should not normally be attempted before 6 months of age. However when testing is clinically necessary, a severe deficiency or function-antigen discrepancy indicating type 2 disease should be apparent. Samples from children are particularly prone to the elevation by stress and if borderline results are obtained they may need to be repeated when the child is older. Modified bleeding scores for use in children are available (Marcus et al., 2011).
Guideline

Recommendations

- A function:antigen ratio of <0.6 should be used to identify patients with type 2 VWD (1B).
- RIPA should be performed on all patients with reduced VWF:RCo/VWF:Ag or VWF:CB/VWF:Ag ratios or when thrombocytopenia is present (1B).
- Multimer analysis should be used to distinguish between types 2A and 2M (1B).
- If multimer analysis is not available then the ratios of VWF:RCo and VWF:CB to VWF:Ag should be used to distinguish types 2A and 2M (1B).

Genetic analysis and family testing

Genetic testing

For many patients, phenotypic analysis yields sufficient information for VWD classification and thus appropriate treatment. However, certain circumstances, indicated below, may warrant VWF analysis to help clarify disease type or risk of disease inheritance, or to facilitate prenatal diagnosis.

Mild or moderate haemophilia A and 2N VWD can be challenging to discriminate, especially in the absence of a family history. The VWF:FVIIIB assay can discriminate between the two disorders, but is not widely available. Analysis of VWF exons 17–25 can identify misense VWF:FVIIIB mutations in patients that have type 2N VWD; individuals lacking these mutations should be investigated for sequence variation in the F8 gene.

Type 2B VWD and PT-VWD patients present with similar phenotypes and can be discriminated by plasma/platelet mixing studies or by genetic analysis. All 2B VWD mutations have been identified between amino acid residues 1266–1461 encoded by exon 28 of VWF whilst PT-VWD mutations affect either the beta hairpin or macroglycopeptide regions of GPIbα encoded by the central region of GPIBA exon 2 (Hamilton et al, 2011). Discrimination using genetic analysis is straightforward and can help guide appropriate therapy.

Prenatal diagnosis is occasionally requested by families with type 3 VWD, particularly where the parents already have one affected child. Mutation analysis of the index case can identify the familial mutation(s), which should be confirmed to be present in each parent and can subsequently be sought in a fetus using chorionic villus or amniocentesis samples. Both sequence and gene dosage analyses may be required to identify the two VWF mutations although mutations are not yet identified in all cases (Keeney et al, 2008).

For those patients where phenotypic analysis does not clarify VWD type, genetic analysis can be used to try and identify explanatory mutation(s), e.g. some patients with D3 domain missense mutations may present with a pleiotropic phenotype with reduced VWF-FVIII binding in addition to reduced VWF-GPIbα binding (Hampshire et al, 2010). Similarly, for some affected individuals without a clear family history of bleeding, VWD inheritance risks for family members are unclear and genetic analysis may help provide clarity through identification of mutation(s) that suggest either dominant or recessive inheritance.

Family testing

When a diagnosis of VWD is made it is appropriate to test first degree relatives with or without a positive bleeding history. In this circumstance, a presumptive diagnosis of VWD may be made on the basis of laboratory findings alone. For patients with ‘low VWF’ (0.3–0.5 iu/ml), family testing may be justifiable depending on bleeding and family history.

Recommendations

- Type 1 VWD should not be excluded in children before the age of 6 months (1B).
- Family testing in VWD is appropriate prior to development of bleeding symptoms (2B).
- Genetic analysis should be used where beneficial to clarify diagnosis and aid management (1B).

Management

Haemostatic therapies

Available therapies to correct haemostasis in VWD comprise the non-concentrate therapies tranexamic acid and desmopressin or concentrates containing either high purity VWF alone or intermediate purity concentrates containing FVIII-VWF.

Desmopressin. The pharmacology and clinical use of desmopressin to temporarily elevate FVIII and VWF levels by releasing endothelial stores have been extensively reviewed and were discussed in the previous version of this guideline (Mannucci, 1997; Pasi et al, 2004). Intravenous, subcutaneous and intranasal desmopressin all have a UK product license for the treatment of VWD.

Desmopressin frequently causes flushing and sometimes hypotension, which are not harmful. Excessive fluid retention should be avoided by limiting fluid intake to 1 l in the subsequent 24 h. Serum sodium should be monitored if desmopressin is used in children <2 years old or whenever repeated doses are given. Desmopressin use has rarely been followed by occlusive arterial events and should not be used in patients who are likely to have atherosclerosis (Federici, 2008).

Because of its clinical utility, and the wide variation in response, a trial of desmopressin should be considered in all
patients with type 1, type 2A, 2M and 2N VWD who do not have a contraindication to its use. It is also useful in patients with bleeding and low VWF as a risk factor ('low VWF'). In type 2B a transient thrombocytopenia frequently follows desmopressin administration (Casonato et al, 1999). This has been regarded as a reason for contraindication and although no harmful effects have been reported, the therapeutic response is usually poor and desmopressin is not recommended for type 2B VWD (Mannucci, 1988; Federici, 2008).

Doses, routes of administration and responses are given in Table II. The magnitude of response will depend on the underlying defect and there are several VWF mutations (including R1205H Vicenza) that have been associated with rapid VWF clearance (Casari et al, 2013): it is therefore important to measure both the peak response at 30–60 min and the maintenance of response at 4–6 h (Millar et al, 2008b; Castaman et al, 2013). However, even when the VWF or FVIII response is shortest, most dental extractions, minor surgeries and deliveries may be successfully managed with desmopressin (Castaman et al, 2011; Trigg et al, 2012).

Desmopressin is relatively contraindicated in children <2 years old. If, after careful consideration, it is to be used in this age group then fluid restriction, avoidance of hypotraemic solutions and close monitoring of serum electrolytes and urine output for at least 24 h after administration is advised.

Tranexamic acid. Tranexamic acid administered topically, as a mouthwash, orally or parenterally remains a useful therapy for minor bleeding or surgery (beginning prior to the procedure) either on its own or as an adjunctive therapy to desmopressin or concentrates. (Pasi et al, 2004).

Recommendations

• A trial of desmopressin should be carried out in patients with type 1, type 2A, 2M and 2N VWD with VWF antigen, activity and FVIII measured at baseline, 30–60 min and 4–6 h (1B).
• When shown to be effective, desmopressin should be used in preference to blood-derived products where possible (1B).

VWF-containing concentrates. A number of plasma-derived concentrates containing VWF are available for replacement therapy in patients whose desmopressin response is inadequate for the relevant bleeding episode or surgical procedure (Batlle et al, 2009). In choosing which concentrate to use, the plasma source, purification and viral inactivation measures should first be considered although all currently available concentrates have an excellent safety record. For haemostatic activity, the relevant characteristics of these concentrates are the multimeric composition of the VWF, reflected in the VWF:RCo/VWF:Ag ratio, and the amount of FVIII contained per unit of VWF. A VWF:RCo/VWF:Ag ratio close to 1 is desirable because it indicates the VWF has normal multimeric structure and adhesive function, but the appropriate amount of FVIII is debatable and will vary according to the circumstance. Some high purity concentrates contain virtually no FVIII and if given alone to a patient with type 3 VWD it will be >12 h before the FVIII level has risen to normal (Goudemand et al, 1998; Borel-Derlon et al, 2007).

Comparison of different concentrates yields a uniform VWF:RCo recovery of 0·021–0·024 (iu/ml)/(U/kg) (Mannucci et al, 1992a) but reveals significant differences in specific activity (function:antigen) and in their content of HMW multimers (Budde et al, 2006; Batlle et al, 2009).

Initial (primary) haemostasis is dependent upon elevation of the plasma VWF:RCo activity to normal, but longer term secure haemostasis is dependent on a normal level of Factor VIII (Mannucci et al, 1987; Sakurai et al, 2006). Because endogenous FVIII production is normal, continued administration of large amounts of FVIII may result in an undesirably high plasma FVIII level.

Recommendations

• For replacement therapy a VWF-containing concentrate manufactured from a safe plasma source with adequate

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Table II. Desmopressin doses and response for VWD.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Suggested formulation</th>
<th>Dose</th>
<th>Peak levels achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous infusion over 30–60 min</td>
<td>4 µg/ml diluted in 100 ml 0·9% NaCl for infusion</td>
<td>0·3 µg/kg</td>
<td>15 min after infusion completed</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>15 µg/ml</td>
<td>0·3 µg/kg</td>
<td>60–90 min after injection</td>
</tr>
<tr>
<td>Intranasal</td>
<td>150 µg per metered spray</td>
<td>&gt;50 kg: 150 µg spray to each nostril</td>
<td>1–4 h after administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤50 kg: single 150 µg spray</td>
<td></td>
</tr>
</tbody>
</table>
viral testing and inactivation procedures should be chosen (1A).

- For treatment of acute bleeding or emergency surgery, a VWF-FVIII concentrate or a combination of high purity FVIII and high purity VWF concentrates should be used (1A).

Treatment of bleeding episodes

Treatment of acute bleeding episodes. Typical bleeding problems in VWD are epistaxes, gum bleeding and menorrhagia. Post-traumatic bleeding can also occur and type 3 patients can develop spontaneous joint or muscle bleeding. When any of these are frequent, self-administration of desmopressin and tranexamic acid can be helpful (Leissinger et al, 2001). If the patient is non-desmopressin responsive, then acute treatment and secondary prophylaxis using concentrates should be considered. Hormonal management of menorrhagia should also be considered, including use of the Mirena coil (Laffan et al, 2004).

Surgery including dentistry. Management of surgery in patients with VWD may be straightforward in those with mild forms of the disease. However, type 3 and type 2 variants may be extremely difficult to manage and there is no guarantee that haemostasis will be achieved even when plasma concentrations have apparently been corrected into the normal range. In these patients, surgery should be carried out in a centre where experienced haematology and laboratory support is available and after careful consultation between responsible teams.

Minor surgery including dental work using an inferior dental block in patients with type 1 disease or ‘low VWF’ (and a minority of 2A and 2M) can often be carried out using desmopressin with or without tranexamic acid. The level of VWF:RCo and FVIII required will vary with the particular procedure but is likely to be satisfactory if >0.5 iu/ml. The response to desmopressin should be measured unless it is well known and also when repeated doses are given. The response to a second dose of desmopressin is, on average, 30% lower than the first but tends not to fall further thereafter (Mannucci et al, 1992b). Particular care is required when the endogenous VWF has a shortened half-life and in patients with type 2N VWD. When desmopressin is contraindicated or the response is inadequate, a VWF-FVIII concentrate should be used. The recovery of both VWF and FVIII is approximately 0.02 iu/ml per kg given.

For major surgery in all types of VWD the VWF:RCo and FVIII should be corrected to ≥1.0 iu/ml preoperatively with either desmopressin or concentrate(s). In the postoperative period, recent studies have shown efficacy by measuring and maintaining VWF:RCo >0.5 iu/ml for 6 d (Mannucci et al, 2013). However, maintaining FVIII >0.5 iu/ml for 7–10 d using a suitable VWF-FVIII concentrate has also proved effective (Windyga et al, 2011) and was common practice before rapid VWF:RCo measurement became available (Lusher, 1998; Mannucci, 2001). It does not appear necessary to correct the bleeding time or PFA100 time and these need not be measured. Surgery should therefore be carried out only in centres with the ability to perform these measurements with the required frequency.

Tranexamic acid remains a useful adjunctive therapy. When bleeding persists despite apparently normal plasma levels of VWF activity, platelet transfusion may be helpful.

Platelet transfusion is also the treatment of choice in platelet-type VWD pseudo (PT-VWD) and may be supplemented by FVIII-VWF concentrate (O’Connor et al, 2011; Othman, 2011).

Recommendations

- Factor VIII levels should be monitored regularly in all major and most minor surgical procedures (1B). The FVIII plasma concentration should be ≥1.0 iu/ml to cover major surgery and sustained above 0.5 iu/ml in the postoperative period (1B).

- The VWF:RCo should be monitored in major surgical procedures, particularly in the perioperative period (grade C, level IV). The VWF:RCo should be maintained above 0.5 iu/ml in the perioperative period (1B).

Prophylactic therapy

Because most cases of VWD are relatively mild and patients do not suffer from serious spontaneous bleeding, prophylaxis is rarely indicated. Exceptions include patients with type 3 disease plus haemarthroses, severe epistaxis, women with menorrhagia, and those with VWD in conjunction with an on-going risk factor for bleeding, such as angiodyplasia. In 2006 an international survey reported that 74.5% type 3, 17.6% type 2 and 7.8% type 1 patients were receiving prophylaxis (Berntorp et al, 2006). The most frequent indications were epistaxis/oral bleeding (23.6%), gastrointestinal (GI) bleeding (23.6%), joint bleeding (21.8%), and menorrhagia (7.3%) (Berntorp et al, 2006). Prophylaxis was able to almost abolish joint bleeding but was less effective against mucosal bleeding (50–60% reduction). A German cohort study also reported that prophylaxis was almost completely effective in abolishing bleeding (Halimeh et al, 2011). Typical doses were 20–50 iu/kg VWF:RCo given 2–3 times per week. In these studies a variety of VWF concentrates were used, but notably, for prophylaxis, a FVIII-containing concentrate may not be necessary. There are no data to indicate the appropriate trough level of FVIII or VWF but analogy with experience in haemophilia seems appropriate. Prophylaxis beginning at age <5 years is reported to prevent arthropathy (Berntorp et al, 2010).
Recommendations

- Prophylaxis should be considered for recurrent bleeding in all types of VWD (1A).
- In children with type 3 VWD, consider prophylaxis 2–3 times per week at 30–50 IU VWF:RCo/kg when joint bleeding develops (as for haemophilia). (1A).
- Intermediate purity FVIII-VWF or high purity VWF concentrates are both appropriate for prophylaxis (1B).

Pregnancy

Levels of VWF and FVIII rise from early in the first trimester of pregnancy and increase with gestational stage, reaching two to three times those of the non-pregnant state at term. Levels start to fall soon after delivery, returning to non-pregnant values within a few weeks (Stirling et al, 1984; Sanchez-Luceros et al, 2003; Mahieu et al, 2007).

Women with VWD whose VWF activity does not rise to normal levels during pregnancy should be delivered in an obstetric unit that can easily and quickly access Haemophilia Centre and comprehensive neonatal care facilities. A plan for management of delivery and the puerperium should be drawn up jointly between the obstetrician and Haemophilia Centre and agreed with the patient. The increase in VWF is often sufficient to correct the VWF deficiency in women with type 1 VWD, but not in qualitative or severe VWF deficiency (Walker et al, 1994; Lee et al, 2006). Pregnancy may exacerbate the thrombocytopenia and bleeding tendency in women with type 2B VWD (Ranger et al, 2012).

Von Willebrand factor parameters should be checked at booking and at around 34 weeks gestation unless levels have already been shown to have risen to normal. Neuraxial anaesthesia, vaginal delivery and Caesarean section can all be regarded as safe in type 1 when VWF:RCo >0.5 IU/ml. In type 2 and 3 VWD, restoration of normal haemostasis is not reliably achievable even following replacement therapy. Therefore, neuraxial anaesthesia is not recommended for use in types 2 or 3 VWD irrespective of whether VWF activity has been restored to apparently normal levels. Patients may require several days’ treatment, especially after Caesarean section. Even if VWF parameters are satisfactory at the time of delivery, abnormal bleeding may ensue following discharge from hospital. It is important that women are made aware of this and advised to seek appropriate medical help should they develop persistent heavy postpartum bleeding. Thromboprophylaxis may be given to patients with adequate correction of VWF parameters.

Desmopressin is safe both in pregnancy and at delivery (Ray, 1998; Trigg et al, 2012) but should be avoided in pre-eclampsia. Repeated administration should be avoided in view of the sensitivity of the fetus to the effects of hyponatraemia.

Tranexamic acid is not contraindicated during pregnancy or the puerperium; a limited quantity (c. 1%) may be secreted in breast milk http://www.medicines.org.uk/emc/medicine/27753, although is unlikely to produce an antifibrinolytic effect in the infant.

Where a fetus is at risk of having significantly reduced plasma VWF activity levels, invasive monitoring procedures, mid-cavity rotational forceps and Ventouse delivery should be avoided with early recourse to Caesarean section. Administration of intramuscular vitamin K therapy can be considered safe, unless the infant is at risk of type 3 VWD.

Recommendations

- All women with type 2 and type 3 VWD, and women with type 1 VWD in whom VWF levels are unlikely to normalize should be delivered in an obstetric unit with close collaboration between haematology, obstetric, anaesthetic and neonatal teams and access to 24-h monitoring of FVIII-VWF (2C).
- The delivery of women with type 1 VWD can be managed as normal when VWF:RCo activity is >0.5 IU/ml by 34–36 weeks gestation (1C).
- Vaginal delivery or Caesarean section can be performed when VWF:RCo activity is maintained >0.5 IU/ml and platelet count maintained >50 x 109/l (2C).
- Neuraxial anaesthesia is not recommended in women with type 2 and type 3 VWD, or in women with type 1 VWD in whom plasma VWF levels have failed to normalize (1B).
- Intermediate or high purity VWF concentrates, desmopressin and tranexamic acid can be used to support haemostasis during pregnancy, delivery and the puerperium (1B).

VWF inhibitors

Von Willebrand factor inhibitors have been described in multi-transfused patients with type 3 VWD at a frequency of 5–10% (James et al, 2013) but not in other VWD subgroups. Patients who develop inhibitors may present with loss of response to VWF concentrate, sometimes with an associated anaphylactic reaction (Mannucci et al, 1987).

Inhibitors to VWF cannot be reliably detected by either conventional mixing tests or ELISA-based assays (James et al, 2013). Poor VWF recovery and/or rapid clearance after infusion of VWF concentrate may therefore be the only indication of an inhibitor.

Treatment options for type 3 VWD patients with inhibitors include recombinant FVIII administered by continuous intravenous infusion at very large doses sufficient to maintain FVIII levels >0.50 IU/ml (Mannucci et al, 1987), recombinant activated FVII (rVIIa) (Ciavarella et al, 1996; Mannucci, 2001; Boadas et al, 2011), platelet transfusions (James et al, 2013) and tranexamic acid. Patients with low-
level inhibitors may still respond to infusions of VWF-containing concentrate but anamnestic responses may be seen. A case of successful immune tolerance in a 9-year-old boy with type 3 VWD and inhibitors has been described (Pergantou et al, 2012).

Recommendations

- Traditional mixing studies are an unreliable method for inhibitor screening in type 3 VWD and measurement of in vivo recovery and survival should be considered if an inhibitor is suspected (2A).
- If there is no response to VWF concentrate or when anaphylaxis occurs, high dose rVIII infusion, rVIIa, platelet transfusion and tranexamic acid should be considered (2A).

Acquired von Willebrand syndrome (AVWS)

Acquired von Willebrand syndrome is the term used to describe an acquired loss of VWF function. It can arise via a wide range of mechanisms and should be suspected when a patient’s current symptoms or laboratory results do not match their clinical history. The AVWS will respond to removal of the cause where this is possible, such as aortic valve replacement, treatment of Wilms tumour or correction of hypothyroidism. Paraproteins causing AVWS are not easily removed but AVWS associated with IgG paraproteins frequently responds to intravenous immunoglobulin (Federici et al, 1998). Other treatment options include VWF concentrates, desmopressin, plasma exchange and immunoabsorption (Tiede et al, 2011).

Topics for audit

Registration for those patients who fulfil diagnostic criteria for VWD.

- Patient registrations with appropriate classification of type entered.
- Proportion of eligible patients who have had test dose of desmopressin administered.
- Proportion of desmopressin test doses that include a measurement of fall-off at 4–6 h.
- Proportion of patients registered with mild haemophilia who have had possible 2N VWD excluded.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UKHCDO, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Author contributions

All authors took an active role in drafting, reviewing and approving the guideline in a series of round table meetings and subsequent correspondence. ML assembled the final draft.

Conflict of interests

ML has received speaker fees from Bayer, Octapharma and Pfizer, advisory board fees from CSL-Behring, Pfizer, Bayer and Grifols and research support from Bayer and CSL Behring. WL has received speaker fees and travel support from CSL and advisory board fees from Octapharma. JSOD has served on the speakers bureau for Baxter, Bayer, Novo Nordisk, Leo Pharma and Octapharma; served on the advisory boards of Baxter, Bayer, Octapharma and Pfizer and received research grant funding awards from Baxter, Bayer and Novo Nordisk. AW has no declarations of interest relating to this guideline. AG has received speaker fees from Octapharma and VWF mutation database support from CSL Behring. CMM has received research grant funding awards from Baxter, Bayer and Novo Nordisk. CM has received research funding from Baxter, CSL Behring, Pfizer and Baxter and served on advisory boards for CSL and NovoNordisk. DMK has served on advisory boards for Baxter, CSL, Bayer, Pfizer and NovoNordisk. RCT has received speaker and/or consultancy fees from Baxter, Pfizer and Bayer.

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to von Willebrand factor. Haemophilia, 18, e66–e67.


von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA)¹


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Summary. von Willebrand disease (VWD) is a commonly encountered inherited bleeding disorder affecting both males and females, causing mucous membrane and skin bleeding symptoms, and bleeding with surgical or other haemostatic challenges. VWD may be disproportionately symptomatic in women of child-bearing age. It may also occur less frequently as an acquired disorder (acquired von Willebrand syndrome). VWD is caused by deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that mediates platelet haemostatic function and stabilizes blood coagulation factor VIII. The pathophysiology, classification, diagnosis and management of VWD are relatively complex, but understanding them is important for proper diagnosis and management of patients with VWD. These evidence-based guidelines for diagnosis and management of VWD from the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel (USA) review relevant publications, summarize current understanding of VWD pathophysiology and classification, and present consensus diagnostic and management recommendations based on analysis of the literature and expert opinion. They also suggest an approach for clinical and laboratory evaluation of individuals with bleeding symptoms, history of bleeding or conditions associated with increased bleeding risk. This document summarizes needs for further research in VWF, VWD and bleeding disorders, including clinical research to obtain more objective information about bleeding symptoms, advancements in diagnostic and therapeutic tools, and enhancement in the education and training of clinicians and scientists in bleeding and thrombotic disorders. The NHLBI Web site (http://www.nhlbi.nih.gov/guidelines/vwd) has a more detailed document, a synopsis of these recommendations, and patient education information.

¹From The Diagnosis, Evaluation and Management of von Willebrand Disease, National Heart, Lung, and Blood Institute, National Institutes of Health (GPO #08-5832), which is available at http://www.nhlbi.nih.gov/guidelines/vwd and from the NHLBI Health Information Center, Bethesda, MD (telephone no. 301-592-8573).

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Keywords: acquired von Willebrand syndrome, bleeding disorder, clotting factor concentrate, coagulation factor VIII, desmopressin, haemorrhage, menorrhagia, platelet disorder, von Willebrand disease, von Willebrand factor

Introduction

von Willebrand disease (VWD) is an inherited bleeding disorder that is caused by deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that mediates the initial adhesion of platelets at sites of vascular injury and also binds and stabilizes blood clotting factor VIII (FVIII) in the circulation. Therefore, defects in VWF can cause bleeding by impairing platelet adhesion or by reducing the concentration of FVIII.

VWD is a relatively common cause of bleeding, but the prevalence varies considerably among studies and depends strongly on the case definition that is used. VWD prevalence has been estimated in several countries on the basis of the number of symptomatic patients seen at haemostasis centres, and the values range from roughly 23 to 110 per million population (0.0023–0.01%) [1].

The prevalence of VWD has also been estimated by screening populations to identify persons with bleeding symptoms, low VWF levels, and similarly affected family members. This population-based approach has yielded estimates for VWD prevalence of 0.6% [2], 0.8% [3] and 1.3% [4] – more than two orders of magnitude higher than the values arrived at by surveys of haemostasis centres.

The discrepancies between the methods for estimating VWD prevalence illustrate the need for better information concerning the relationship between VWF levels and bleeding. Many bleeding symptoms are exacerbated by defects in VWF, but the magnitude of the effect is not known. For example, approximately 12% of women who have menstrual periods have excessive menstrual bleeding [5]. This fraction is much higher among women with VWD, but it also appears to be increased for women who have VWF levels at the lower end of the normal range. Quantitative data on these issues would allow a more informed approach to the diagnosis and management of VWD and could have important implications for medical practice and for public health.

In addition to the need for better information about VWD prevalence and the relationship of low VWF levels to bleeding symptoms or risk, there are needs for enhancing knowledge and improving clinical and laboratory diagnostic tools for VWD. Also needed are better knowledge of and treatment options for management of VWD and bleeding or bleeding risk. As documented in this VWD guidelines publication, published studies are lacking to support some of the recommendations that, therefore, are based mainly on Expert Panel opinion.

Guidelines for VWD diagnosis and management, based on the evidence from published studies, the opinions of experts, or both, have been published for practitioners in Canada [6], Italy [7] and the United Kingdom [8,9], but not in the United States. The VWD guidelines from the US Expert Panel are based on review of published evidence as well as expert opinion. Users of these guidelines should be aware that individual professional judgment is not abrogated by recommendations in these guidelines.

These guidelines for diagnosis and management of VWD were developed for practicing primary care and specialist clinicians — including family physicians, internists, obstetrician–gynaecologists, paediatricians, and nurse practitioners — as well as haematologists and laboratory medicine specialists. The National Heart, Lung, and Blood Institute (NHLBI) Web site [10] has a synopsis of these recommendations, patient education information, and a more detailed document that includes additional background information. Also on the Web site are 13 evidence tables that summarize published information supporting recommendations that are graded as B or higher and have two or more references.

Project history and methods

During spring 2004, the NHLBI began planning for the development of clinical practice guidelines for VWD. In consultation with the American Society of Hematology, the institute convened an Expert Panel on VWD, chaired by William L. Nichols MD. The Expert Panel members were selected to provide expertise in basic sciences, clinical and laboratory diagnosis, evidence-based medicine, and the clinical management of VWD, including specialists in haematology as well as family medicine, obstetrics and gynaecology, paediatrics, internal medicine and laboratory sciences. The Expert Panel comprised one basic scientist and nine physicians — including one family physician, one obstetrician–gynaecologist and
seven haematologists with expertise in VWD (two were paediatric haematologists). Ad hoc members of the Panel represented the Division of Blood Diseases and Resources of the NHLBI. The Panel was coordinated by the Office of Prevention, Education, and Control of the NHLBI. Panel members disclosed, verbally and in writing, any financial conflicts.

Barbara M. Alving MD, then acting director of the NHLBI, gave the charge to the Expert Panel to examine the current science in the area of VWD and to come to consensus regarding clinical recommendations for diagnosis, treatment and management of this common inherited bleeding disorder. The Panel was also charged to base each recommendation on current science and to indicate the strength of the relevant literature for each recommendation.

The development of this report was funded entirely by the NHLBI, National Institutes of Health (NIH). Panel members and reviewers participated as volunteers and were compensated only for travel expenses related to three in-person Expert Panel meetings.

After the Expert Panel finalized a basic outline for the guidelines, members were assigned to the three main sections: (i) Introduction and Background, (ii) Diagnosis and Evaluation, and (iii) Management of VWD. Three members were assigned lead responsibility for each section. The section groups were responsible for developing detailed outlines for the sections, reviewing the pertinent literature, writing the sections and drafting recommendations with the supporting evidence for the full Panel to review.

After internal NHLBI/NIH review of the draft document, it was posted on the NHLBI Web site for public review and comments. The draft was then revised by the Expert Panel in response to external review comments. The final document underwent NHLBI/NIH review before posting on the NHLBI Web site as well as finalization of a modified version for scientific journal publication.

**Literature searches**

Three section outlines, approved by the Expert Panel chair, were used as the basis for compiling relevant search terms, using the Medical Subject Headings (MeSH terms) of the MEDLINE database. If appropriate terms were not available in MeSH, then relevant non-MeSH key words were used. In addition to the search terms, inclusion and exclusion criteria were defined on the basis of feedback from the Panel about specific limits to include in the search strategies, specifically the following:

1. date restriction: 1990–2004;
2. language: English; and
3. study/publication types: randomized-controlled trial; meta-analysis; controlled clinical trial; epidemiological studies; prospective studies; multicentre study; clinical trial; evaluation studies; practice guideline; review, academic; review, multicare; technical report; validation studies; review of reported cases; case reports; journal article (to exclude letters, editorials, news, etc.).

The search strategies were constructed and executed in the MEDLINE database as well as in the Cochrane Database of Systematic Reviews to compile a set of citations and abstracts for each section. Initial searches on specific key word combinations and date and language limits were further refined by using the publication type limits to produce results that more closely matched the section outlines. Once the section results were compiled, the results were put in priority order by study type as follows:

1. randomized-controlled trial;
2. meta-analysis (quantitative summary combining results of independent studies);
3. controlled clinical trial;
4. multicentre study;
5. clinical trial (includes all types and phases of clinical trials);
6. evaluation studies;
7. practice guideline (for specific healthcare guidelines);
8. epidemiological studies;
9. prospective studies;
10. review, academic (comprehensive, critical, or analytical review);
11. review, multicare (review with epidemiological applications);
12. technical report;
13. validation studies;
14. review of reported cases (review of known cases of a disease); and
15. case reports.

On examination of the yield of the initial literature search, it was determined that important areas in the section outlines were not addressed by the citations, possibly because of the date delimiters. In addition, Panel members identified pertinent references from their own searches and databases, including landmark references predating the 1990 date restriction, and 2005 and 2006 references (to October 2006). Therefore, additional follow-up database searching was done using the same search strategies from the initial round, but covering dates before 1990 and during 2005 and 2006 to double-check for key studies appearing in the literature.
outside the limits of the original range of dates. Also, refined searches in the 1990–2006 date range were conducted to analyse the references used by Panel members that had not appeared in the original search results. These revised searches helped round out the database search to provide the most comprehensive approach possible. As a result, the references used in the guidelines included those retrieved from the two literature searches combined with the references suggested by the Panel members. These references inform the guidelines and clinical recommendations, on the basis of the best available evidence in combination with the Panel’s expertise and consensus.

**Clinical recommendations – grading and levels of evidence**

Recommendations made in this document are based on the levels of evidence described in Table 1, with a priority grading system of A, B or C. Grade A is reserved for recommendations based on evidence levels Ia and Ib. Grade B is given for recommendations having evidence levels of IIa, IIb and III. Grade C is for recommendations based on evidence level IV [8]. None of the recommendations merited a grade of A. Evidence tables are available on the NHLBI Web site for those recommendations graded as B with two or more references [10].

<table>
<thead>
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<th>Level</th>
<th>Type of evidence</th>
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<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomized-controlled trials</td>
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<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomized-controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td>
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<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities</td>
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**Scientific overview**

**Discovery and identification of VWD/VWF**

The patient who led to the discovery of a hereditary bleeding disorder that we now call ‘von Willebrand disease’ was a 5-year-old girl who lived on the Aland Islands and was brought to Deaconess Hospital in Helsinki, Finland, in 1924 to be seen by Dr Erik von Willebrand [11]. He ultimately assessed 66 members of her family and reported in 1926 that this was a previously undescribed bleeding disorder that differed from haemophilia and exhibited (i) mucocutaneous bleeding, (ii) autosomal inheritance rather than being linked to the X chromosome, (iii) prolonged bleeding times (BT) by the Duke method (earlobe BT) and (iv) normal clotting time. Not only did he recognize the autosomal inheritance pattern, he also recognized that bleeding symptoms were greater in children and in women of child-bearing age. He subsequently found that blood transfusions were useful not only to correct the anaemia, but also to control bleeding.

In the 1950s, it became clear that a ‘plasma factor’, antihaeimophilic factor (factor VIII [FVIII]), was decreased in these persons and that Cohn fraction I-0 could correct both the plasma deficiency of FVIII and the prolonged BT. For the first time, the factor causing the long BT was called ‘von Willebrand factor’. As cryoprecipitate and commercial FVIII concentrates were developed, it was recognized that both VWF and antihaeimophilic factor (FVIII) purified together.

When immunoassays were developed, persons who had VWD (in contrast to those who had haemophilia A) were found to have reduced factor VIII-related antigen (FVIIIIR:Ag), which we now refer to as von Willebrand factor antigen (VWF:Ag). Characterization of the proteins revealed that FVIII was the clotting protein deficient in haemophilia A, and VWF was a separate FVIII carrier protein that resulted in the cofractionation of both proteins in commercial concentrates. Furthermore, a deficiency of VWF resulted in increased FVIII clearance because of the reduced carrier protein, VWF.

Since the 1980s, molecular and cellular studies have defined haemophilia A and VWD more precisely. Persons who had VWD had a normal FVIII gene on the X chromosome, but some were found to have an abnormal VWF gene on chromosome 12. Variant forms of VWF were recognized in the 1970s, and these variations are now recognized as the result of synthesis of an abnormal protein. Gene sequencing identified many of these persons as having a VWF...
gene mutation. The genetic causes of milder forms of low VWF are still under investigation, and these forms may not always be caused by an abnormal VWF gene. In addition, acquired disorders may result in reduced or dysfunctional VWF (discussed in a later section, Acquired von Willebrand Syndrome). Table 2 summarizes VWF designations, properties and assays. Table 3 lists and defines abbreviations used in the text of this document.

The VWF protein and its functions in vivo

VWF is synthesized in two cell types. In the vascular endothelium, VWF is synthesized and subsequently stored in secretory granules (Weibel-Palade bodies) from which it can be released by stress or drugs such as desmopressin (1-desamino-8-D-arginine, DDAVP; Sanofi-Aventis US, Bridgewater, NJ, USA), a synthetic analogue of vasopressin. VWF is also synthesized in bone marrow megakaryocytes where it is stored in platelet alpha-granules from which it is released after platelet activation. Desmopressin does not release platelet VWF.

VWF is a protein that is assembled from identical subunits into linear strings of varying size referred to as multimers. These multimers can be larger than 20 million daltons in mass and more than 2 μm long. The complex cellular processing consists of dimerization in the endoplasmic reticulum, glycosylation in the endoplasmic reticulum and Golgi complex, multimerization in the Golgi complex, and packaging into storage granules. The latter two processes are under the control of the VWF propeptide (VWFpp), which is cleaved from VWF at the time of storage. VWF that is released acutely into the circulation is accompanied by a parallel rise in FVIII, but it is still not entirely clear whether this protein–protein association first occurs within the endothelial cell [12,13].

In plasma, the FVIII–VWF complex circulates as a loosely coiled protein complex that does not interact strongly with platelets or endothelial cells under basal conditions. When vascular injury occurs, VWF becomes tethered to the exposed subendothelium (collagen, etc.). The high fluid shear rates that occur in the microcirculation appear to induce a conformational change in multimeric VWF that causes platelets to adhere, become activated, and then aggregate so as to present an activated platelet phospholipid surface. This facilitates clotting that is regulated in part by FVIII. Because of the specific characteristics of haemostasis and fibrinolysis on mucosal surfaces, symptoms in VWD are often greater in these tissues.

Plasma VWF is primarily derived from endothelial synthesis. Platelet and endothelial cell VWF are released locally after cellular activation where this VWF participates in the developing haemostatic plug or thrombus (Fig. 1).

Plasma VWF has a half-life of approximately 12 h (range: 9–15). VWF is present as very large multimers that are subjected to physiological degradation

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**Table 2. Synopsis of VWF designations, properties and assays.**

<table>
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<th>Designation</th>
<th>Property</th>
<th>Assay</th>
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<tr>
<td>VWF</td>
<td>Multimeric glycoprotein that promotes platelet adhesion and aggregation and is a carrier for FVIII in plasma</td>
<td>See specific VWF assays below</td>
</tr>
<tr>
<td>VWF:RCo</td>
<td>Binding activity of VWF that causes binding of VWF to platelets in the presence of ristocetin with consequent agglutination</td>
<td>Ristocetin cofactor activity; quantitates platelet agglutination after addition of ristocetin and VWF</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>VWF protein as measured by protein assays; does not imply functional ability</td>
<td>Immunological assays such as ELISA, LIA, RIA, Laurell electroimmunoassay</td>
</tr>
<tr>
<td>VWF:CB</td>
<td>Ability of VWF to bind to collagen</td>
<td>Collagen-binding activity; quantitates binding of VWF to collagen-coated ELISA plates</td>
</tr>
<tr>
<td>VWF multimers</td>
<td>Size distribution of VWF multimers as assessed by agarose gel electrophoresis</td>
<td>VWF multimer assay; electrophoresis in agarose gel and visualization by monospecific antibody to VWF</td>
</tr>
<tr>
<td>FVIII</td>
<td>Circulating coagulation protein that is protected from clearance by VWF and is important in thrombin generation</td>
<td>FVIII activity; plasma clotting test based on PTT assay using FVIII-deficient substrate; quantitates activity</td>
</tr>
<tr>
<td>RIPA</td>
<td>Test that measures the ability of a person's VWF to bind to platelets in the presence of various concentrations of ristocetin</td>
<td>RIPA: aggregation of a person's PRP to various concentrations of ristocetin</td>
</tr>
</tbody>
</table>

ELISA, enzyme-linked immunosorbent assay; FVIII, factor VIII; LIA, latex immunoassay (automated); PRP, platelet-rich plasma; PTT, activated partial thromboplastin time; RIA, radioimmunoassay; RIPA, ristocetin-induced platelet aggregation; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand factor collagen-binding activity; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
A Disintegrin-like Metalloprotease domain (reprolysin type) with ThromboSpondin type 1 motif, member 13: a plasma metalloprotease that cleaves multimeric VWF 

Acquired von Willebrand (disease) syndrome

Bleeding time

Complete blood cell count

Coefficient of variation

Dilation and curettage

1-Desamino-8-arginine; desmopressin

Deep vein thrombosis

Enzyme-linked immunosorbent assay

Food and Drug Administration

Factor VIII-related antigen (see VWF:Ag)

Glycoprotein Ib (platelet)

Immune globulin intravenous (also known as IVIG)

International Society on Thrombosis and Haemostasis

International Unit

i.v.

Latex immunoassay (automated)

Medical Subject Headings (in MEDLINE)

Monoclonal gammopathy of uncertain significance

National Heart, Lung, and Blood Institute

National Institutes of Health

Non-steroidal anti-inflammatory drug

Polymerase chain reaction

Platelet function analyzer

Platelet-type von Willebrand disease

Partial thromboplastin time (activated partial thromboplastin time)

Ristocetin-induced platelet aggregation

s.c.

Thrombotic thrombocytopenic purpura

Tissue plasminogen activator

von Willebrand disease

von Willebrand factor (FVIII carrier protein)

von Willebrand factor antigen

von Willebrand factor collagen-binding activity

von Willebrand factor: factor VIII-binding assay

von Willebrand factor platelet-binding assay

von Willebrand factor propeptide

von Willebrand factor ristocetin cofactor activity

World Health Organization

Table 3. Nomenclature and abbreviations*

<table>
<thead>
<tr>
<th>Designation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS13</td>
<td>A Disintegrin-like Metalloprotease domain (reprolysin type) with ThromboSpondin type 1 motif, member 13: a plasma metalloprotease that cleaves multimeric VWF</td>
</tr>
<tr>
<td>AVWS</td>
<td>Acquired von Willebrand (disease) syndrome</td>
</tr>
<tr>
<td>BT</td>
<td>Bleeding time</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood cell count</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
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<tr>
<td>D&amp;C</td>
<td>Dilation and curettage</td>
</tr>
<tr>
<td>DDAVP</td>
<td>1-Desamino-8-arginine; desmopressin</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FVIII</td>
<td>Factor VIII [blood clotting] factor VIII</td>
</tr>
<tr>
<td>FVIII:Ag</td>
<td>Factor VIII-related antigen (see VWF:Ag)</td>
</tr>
<tr>
<td>GPIb</td>
<td>Glycoprotein Ib (platelet)</td>
</tr>
<tr>
<td>IGIV</td>
<td>Immune globulin intravenous (also known as IVIG)</td>
</tr>
<tr>
<td>ISTH</td>
<td>International Society on Thrombosis and Haemostasis</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenously</td>
</tr>
<tr>
<td>LIA</td>
<td>Latex immunoassay (automated)</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings (in MEDLINE)</td>
</tr>
<tr>
<td>MGUS</td>
<td>Monoclonal gammopathy of uncertain significance</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PFA-100</td>
<td>Platelet function analyzer</td>
</tr>
<tr>
<td>PLT-VWD</td>
<td>Platelet-type von Willebrand disease</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time (activated partial thromboplastin time)</td>
</tr>
<tr>
<td>RIPA</td>
<td>Ristocetin-induced platelet aggregation</td>
</tr>
<tr>
<td>s.c.</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>TTP</td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>VWD</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>VWF</td>
<td>von Willebrand factor (FVIII carrier protein)</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>von Willebrand factor antigen</td>
</tr>
<tr>
<td>VWF:CB</td>
<td>von Willebrand factor collagen-binding activity</td>
</tr>
<tr>
<td>VWF:FVIIIIB</td>
<td>von Willebrand factor: factor VIII-binding assay</td>
</tr>
<tr>
<td>VWF:PB</td>
<td>von Willebrand factor platelet-binding assay</td>
</tr>
<tr>
<td>VWFpp</td>
<td>von Willebrand factor propeptide</td>
</tr>
<tr>
<td>VWF:RCO</td>
<td>von Willebrand factor ristocetin cofactor activity</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

*Abbreviations listed appear in the text. Abbreviations in the tables are expanded in each table's footnotes.

**These abbreviations (for FVIII and VWF and all their properties) are defined in Marder et al. [397] and Mazurier and Rodeghiero [398].

by the metalloprotease ADAMTS13 [A Disintegrin-like And Metalloprotease domain (reprolysin type) with ThromboSpondin type 1 motif, member 13]. Deficiency of ADAMTS13 is associated with the pathological microangiopathy of thrombotic thrombocytopenic purpura (TTP). The most common variant forms of type 2A VWD are characterized by increased VWF susceptibility to ADAMTS13.

Factors affecting VWF levels Factors that affect levels of plasma VWF include age, race, ABO and Lewis blood groups, epinephrine, inflammatory mediators, and endocrine hormones (particularly those associated with the menstrual cycle and pregnancy). VWF is increased during pregnancy (a three- to fivefold elevation over a woman’s baseline by the third trimester) with ageing and with acute stress or inflammation. Africans and African-Americans have higher average levels of VWF than the White or caucasian populations [14,15]. VWF is reduced by hypothyroidism and rarely by autoantibodies to VWF. The rate of VWF synthesis probably is not affected by blood group; however, the survival of VWF appears to be reduced in individuals who have type O blood. In fact, ABO blood group substance has been identified on VWF.

The genetics of VWD

Since the 1980s, molecular and cellular studies have defined haemophilia A and VWD more precisely. Persons with severe VWD have a normal FVIII gene on the X chromosome, and some are found to have an abnormal VWF gene on chromosome 12. The VWF gene is located near the tip of the short arm of chromosome 12, at 12p13.3 [16]. It spans approximately 178 kb of DNA and contains 52 exons [17]. Intron–exon boundaries tend to delimit structural domains in the protein, and introns often occur at similar positions within the gene segments that encode homologous domains. Thus, the structure of the VWF gene reflects the mosaic nature of the protein (Fig. 2).

A partial, unprocessed VWF pseudogene is located at chromosome 22q11.2 [18]. This pseudogene spans approximately 25 kb of DNA and corresponds to exons 23–34 and part of the adjacent introns of the VWF gene [19]. This segment of the gene encodes domains A1A2A3, which contain binding sites for platelet glycoprotein Ib (GPIb) and collagen, as well as the site cleaved by ADAMTS13. The VWF pseudogene and gene have diverged 3.1% in DNA sequence, consistent with a relatively recent origin of the pseudogene by partial gene duplication [19]. This pseudogene is found in humans and great apes (bonobo, chimpanzee, gorilla and orangutan) but not in more distantly related primates [20]. The VWF pseudogene complicates the detection of VWF gene mutations because polymerase chain reactions

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Fig. 1. von Willebrand factor (VWF) and normal haemostasis. A blood vessel cross-section shows stages of normal haemostasis. Top, VWF is the carrier protein for blood clotting factor VIII (FVIII). Under normal conditions VWF does not interact with platelets or the blood vessel wall that is covered with endothelial cells. Middle left, After vascular injury, VWF adheres to the exposed subendothelial matrix. Middle right, After VWF is uncoiled by local shear forces, platelets adhere to the altered VWF, and these platelets undergo activation and recruit other platelets to this injury site. Bottom left, The activated and aggregated platelets alter their membrane phospholipids exposing phosphatidylserine, and this activated platelet surface binds clotting factors from circulating blood and initiates blood clotting on this surface where fibrin is locally deposited. Bottom right, The combination of clotting and platelet aggregation and adhesion forms a platelet-fibrin plug, which results in the cessation of bleeding. The extent of the clotting is carefully regulated by natural anticoagulants. Subsequently, thrombolysis initiates tissue repair, and ultimately the vessel may be re-endothelialized and blood flow maintained. (Courtesy of R. R. Montgomery, the BloodCenter of Wisconsin and Medical College of Wisconsin, Milwaukee, Wisconsin; used with permission).

Fig. 2. Structure and domains of von Willebrand factor (VWF). The VWF protein sequence [amino acid (aa) 1–2813] is aligned with the cDNA sequence (nucleic acid 1–8439). The VWF signal peptide is the first 22 aa, the propeptide (VWFpp) is aa 23–763 and mature VWF is aa 764–2800. Type 2 mutations are primarily located in specific domains (regions) along the VWF protein. Types 2A, 2B and 2M VWF mutations are primarily located within exon 28 that encodes for the A1 and A2 domains of VWF. The two different types of 2A are those that have increased proteolysis (2A2) and those with abnormal multimer synthesis (2A1). Type 2N mutations are located within the D’ and D3 domains. Ligands that bind to certain VWF domains are identified, including factor VIII (FVIII), heparin, platelet glycoprotein Ib complex (GPIb), collagen and platelet glycoprotein Ib/IIa complex (GPIb/IIa) that binds to the RGD (arginine-glycine-aspartate) amino acid sequence in VWF. (Courtesy of R. R. Montgomery, the BloodCenter of Wisconsin and Medical College of Wisconsin, Milwaukee, Wisconsin; used with permission.)

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(PCRs) can inadvertently amplify segments from either or both loci, but this difficulty can be overcome by careful design of gene-specific PCR primers [19].

The VWF pseudogene may occasionally serve as a reservoir of mutations that can be introduced into the VWF locus. For example, some silent and some potentially pathogenic mutations have been identified in exons 27 and 28 of the VWF gene of persons who have VWD. These same sequence variations occur consecutively in the VWF pseudogene and might have been transferred to the VWF by gene conversion [21–23]. The segments involved in the potential gene conversion events are relatively short, from a minimum of seven nucleotides [21] to a maximum of 385 nucleotides [23]. The frequency of these potential interchromosomal exchanges is unknown.

The spectrum of VWF gene mutations that cause VWD is similar to that of many other human genetic diseases and includes large deletions, frameshifts from small insertions or deletions, splice-site mutations, nonsense mutations causing premature termination of translation, and missense mutations affecting single amino acid residues. A database of VWF mutations and polymorphisms has been compiled for the International Society on Thrombosis and Haemostasis (ISTH) [24,25] and is maintained for online access at the University of Sheffield [26]. Mutations causing VWD have been identified throughout the VWF gene. In contrast to haemophilia A, in which a single major gene rearrangement causes a large fraction of severe disease, no such recurring mutation is common in VWD. There is a good correlation between the location of mutations in the VWF gene and the subtype of VWD, as discussed in more detail in the next section, Classification of VWD Subtypes. In selected families, this information can facilitate the search for VWF mutations by DNA sequencing.

**Classification of VWD subtypes**

VWD is classified on the basis of criteria developed by the VWF Subcommittee of the ISTH, first published in 1994 and revised in 2006 (Table 4) [27,28].

The classification was intended to be clinically relevant to the treatment of VWD. Diagnostic categories were defined that encompassed distinct pathophysiological mechanisms and correlated with the response to treatment with desmopressin or blood products. The classification was designed to be conceptually independent of specific laboratory testing procedures, although most of the VWD subtypes could be assigned by using tests that were widely available. The 1994 classification reserved the designation of VWD for disorders caused by mutations within the VWF gene [28], but this criterion has been dropped from the 2006 classification [27] because, in practice, it is verifiable for only a small fraction of patients.

VWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2) and total deficiency (type 3). Type 2 VWD is divided further into four variants (2A, 2B, 2M and 2N) on the basis of details of the phenotype. Before publication of the 1994 revised classification of VWD [28], VWD subtypes were classified using roman numerals (types I, II, and III), generally corresponding to types 1, 2 and 3 in the 1994 classification, and within type II several subtypes existed (designated by adding sequential letters of the alphabet, i.e. II-A through II-I). Most of the latter VWD variants were amalgamated as type 2A in the 1994 classification, with the exception of type 2B (formerly II-B), for which a separate new classification was created. In addition, a new subtype (2M, with ‘M’ representing ‘multimer’) was created to include variants with decreased platelet-dependent function [VWF ristocetin cofactor activity (VWF:RCo)] but no significant decrease of higher molecular weight VWF multimers (which may or may not have other aberrant structure). Subtype 2N VWD was defined, with ‘N’ representing ‘Normandy’, where the first individuals were identified, with decreased FVIII because of VWF defects of FVIII binding.

Type 1 VWD affects approximately 75% of symptomatic persons who have VWD (see Castaman et al. [29] for a review). Almost all the remaining persons are divided among the four type 2 variants,
and the partitioning among them varies considerably among centres. In France, for example, patients’ distribution has been reported to be 30% type 2A, 28% type 2B, 8% type 2M (or unclassified) and 34% type 2N [30]. In Bonn, Germany, the distribution has been reported to be 74% type 2A, 10% type 2B, 13% type 2M and 3.5% type 2N [31]. Table 5 summarizes information about inheritance, prevalence and bleeding propensity in persons who have different types of VWD.

The prevalence of type 3 VWD in the population is not known precisely but has been estimated (per million population) as 0.55 for Italy [32], 1.38 for North America [33], 3.12 for Sweden [32] and 3.2 for Israel [34]. The prevalence may be as high as 6 per million where consanguinity is common [1].

**Type 1 VWD** Type 1 VWD is found in persons who have partial quantitative deficiency of VWF. The level of VWF in plasma is low, and the remaining VWF mediates platelet adhesion normally and binds FVIII normally. Laboratory evaluation shows concordant decreases in VWF protein concentration (VWF:Ag) and assays of VWF function (VWF:RCo). Levels of blood clotting FVIII usually parallel VWF and may be reduced secondary to reduced VWF. Usually, in type 1 VWD, the FVIII/VWF:Ag ratio is 1.5–2.0. In most persons with type 1 VWD, this results in normal or mildly decreased FVIII, not reduced as much as the VWF. VWF multimer gels show no significant decrease in large VWF multimers [28]. The laboratory evaluation of VWD is discussed in the Diagnosis and Evaluation section.

The spectrum of mutations occurring in VWD type 1 has been described extensively in two major studies [35,36]. Particularly severe, highly penetrant forms of type 1 VWD may be caused by dominant VWF mutations that interfere with the intracellular transport of dimeric proVWF [37–41] or that promote the rapid clearance of VWF from the circulation [40,42,43]. Persons who have such mutations usually have plasma VWF levels <20 IU dL\(^{-1}\) (International Units per deciliter) [35,36]. Most of the mutations characterized to date cause single amino acid substitutions in domain D3 [37–39,41,44]. One mutation associated with rapid clearance has been reported in domain D4 [40].

Increased clearance of VWF from the circulation in type 1 VWD may account for the exaggerated but unexpectedly brief responses to desmopressin observed in some patients. Consequently, better data on the prevalence of increased clearance could affect the approach to diagnosing type 1 VWD and the choice of treatment for bleeding.

A diagnosis of type 1 VWD is harder to establish when the VWF level is not markedly low but instead is near the lower end of the normal range. Type 1 VWD lacks a qualitative criterion by which it can be recognized and instead relies only on quantitative decrements of protein concentration and function. VWF levels in the healthy population span a wide range of values. The mean level of plasma VWF is 100 IU dL\(^{-1}\), and approximately 95% of plasma VWF levels lie between 50 and 200 IU dL\(^{-1}\) [45,46]. Because mild bleeding symptoms are common in the healthy population, the association of bleeding symptoms with a moderately low VWF level may be coincidental [47]. The conceptual and practical issues associated with the evaluation of moderately low VWF levels are discussed more completely later in this section. (See section Type 1 VWD vs. Low VWF: VWF Level as a Risk Factor for Bleeding.)

**Type 2 VWD** The clinical features of several type 2 VWD variants are distinct from those of type 1 VWD, and they can have strikingly distinct and specific therapeutic needs. As a consequence, the medical care of patients with type 2 VWD benefits from the participation of a haematologist who has expertise in haemostasis. Bleeding symptoms in type 2 VWD are often thought to be more severe than those in type 1 VWD, although this impression needs to be evaluated in suitable clinical studies.

**Type 2A VWD.** Type 2A VWD refers to qualitative variants in which VWF-dependent platelet adhesion is decreased because the proportion of large VWF multimers is decreased. Levels of VWF:Ag and FVIII may be normal or modestly decreased, but VWF function is abnormal, as shown by markedly decreased VWF:RCo [48]. Type 2A
VWD may be caused by mutations that interfere with the assembly or secretion of large multimers or by mutations that increase the susceptibility of VWF multimers to proteolytic degradation in the circulation [49–51]. The deficit of large multimers predisposes persons to bleed.

The location of type 2A VWD mutations sometimes can be inferred from high-resolution VWF multimer gels. For example, mutations that primarily reduce multimer assembly lead to the secretion of multimers that are too small to engage platelets effectively and therefore are relatively resistant to proteolysis by ADAMTS13. Homozygous mutations in the propeptide impair multimer assembly in the Golgi complex and give rise to a characteristic ‘clean’ pattern of small multimers that lack the satellite bands usually associated with proteolysis (see Diagnosis and Evaluation section); this pattern was initially described as ‘type IIC’ VWD [52–54]. Heterozygous mutations in the cysteine knot domain can impair dimerization of proVWF in the endoplasmic reticulum and cause a recognizable multimer pattern originally referred to as ‘type IID’ [55,56]. A mixture of monomers and dimers arrives in the Golgi complex, where the incorporation of monomers at the end of a multimer prevents further elongation. As a result, the secreted small multimers contain minor species with an odd number of subunits that appear as faint bands between the usual species that contain an even number of subunits. Heterozygous mutations in cysteine residues of the D3 domain can also impair multimer assembly, but these mutations often also produce an indistinct or ‘smeary’ multimer pattern referred to as ‘type IIE’ [57,58].

In contrast to mutations that primarily affect multimer assembly, mutations within or near the A2 domain of VWF cause type 2A VWD, which is associated with markedly increased proteolysis of the VWF subunits [58] (Fig. 2). These mutations apparently interfere with the folding of the A2 domain and make the Tyr1605–Met1606 bond accessible to ADAMTS13 even in the absence of increased fluid shear stress. Two subgroups of this pattern have been distinguished: group I mutations enhance proteolysis by ADAMTS13 and also impair multimer assembly, whereas group II mutations enhance proteolysis without decreasing the assembly of large VWF multimers [51]. Computer modelling of domain A2 suggests that group I mutations affect both assembly and proteolysis, because group I mutations have a more disruptive effect on the folding of domain A2 than do group II mutations [59].

Type 2B VWD. Type 2B VWD is caused by mutations that pathologically increase platelet-VWF binding, which leads to the proteolytic degradation and depletion of large, functional VWF multimers [58,60]. Circulating platelets are also coated with mutant VWF, which may prevent the platelets from adhering at sites of injury [61].

Although laboratory results for type 2B VWD may be similar to those in type 2A or type 2M VWD, patients with type 2B VWD typically have thrombocytopenia that is exacerbated by surgery, pregnancy or other stress [62–64]. The thrombocytopenia probably is caused by reversible sequestration of VWF-platelet aggregates in the microcirculation. These aggregates are dissolved by the action of ADAMTS13 and VWF, causing the characteristic decrease of large VWF multimers and the prominent satellite banding pattern that indicates increased proteolytic degradation [65,66]. The diagnosis of type 2B VWD depends on finding abnormally increased ristocetin-induced platelet aggregation (RIPA) at low concentrations of ristocetin.

Type 2B VWD mutations occur within or adjacent to VWF domain A1 [24,57,67–70], which changes conformation when it binds to platelet GPIb [71]. The mutations appear to enhance platelet binding by stabilizing the bound conformation of domain A1.

Type 2M VWD. Type 2M VWD includes variants with decreased VWF-dependent platelet adhesion that is not caused by the absence of high-molecular-weight VWF multimers. Instead, type 2M VWD mutations reduce the interaction of VWF with platelet GPIb or with connective tissue and do not substantially impair multimer assembly. Screening laboratory results in type 2M VWD and type 2A VWD are similar, and the distinction between them depends on multimer gel electrophoresis [69].

Mutations in type 2M VWD have been identified in domain A1 (Fig. 2), where they interfere with binding to platelet GPIb [24,57,69,72–74]. One family has been reported in which a mutation in VWF domain A3 reduces VWF binding to collagen, thereby reducing platelet adhesion and possibly causing type 2M VWD [75].

Type 2N VWD. Type 2N VWD is caused by VWF mutations that impair binding to FVIII, lowering FVIII levels so that type 2N VWD masquerades as an autosomal recessive form of haemophilia A [76–78]. In typical cases, the FVIII level is <10% (IU dL−1), with a normal VWF:Ag and VWF:RCo. Discrimination from haemophilia A may require assays of FVIII-VWF binding [79,80].

Most mutations that cause type 2N VWD occur within the FVIII binding site of VWF (Fig. 2), which lies between residues Ser764 and Arg1035 and spans
domain D’ and part of domain D3 [24,81,82]. The most common mutation, Arg854Gln, has a relatively mild effect on FVIII binding and tends to cause a less severe type 2N VWD phenotype [79]. Some mutations in the D3 domain C-terminal of Arg1035 can reduce FVIII binding [83–85], presumably through an indirect effect on the structure or accessibility of the binding site.

Type 3 VWD Type 3 VWD is characterized by undetectable VWF protein and activity, and FVIII levels usually are very low (1–9 IU dL⁻¹) [86–88]. Nonsense and frameshift mutations commonly cause type 3 VWD, although large deletions, splice-site mutations and missense mutations can also do so. Mutations are distributed throughout the VWF gene, and most are unique to the family in which they were first identified [24,89,90].

A small fraction of patients with type 3 VWD develop alloantibodies to VWF in response to the transfusion of plasma products. These antibodies have been reported in 2.6–9.5% of patients with type 3 VWD, as determined by physician surveys or screening [87,91]. The true incidence is uncertain, however, because of unavoidable selection bias in these studies. Anti-VWF alloantibodies can inhibit the haemostatic effect of blood product therapy and also may cause life-threatening allergic reactions [87,92]. Large deletions in the VWF gene may predispose patients to this complication [91].

VWD classification, general issues The principal difficulties in using the current VWD classification concern how to define the boundaries between the various subtypes through laboratory testing. In addition, some mutations have pleiotropic effects on VWF structure and function, and some persons are compound heterozygous for mutations that cause VWD by different mechanisms. This heterogeneity can produce complex phenotypes that are difficult to categorize. Clinical studies of the relationship between VWD genotype and clinical phenotype would be helpful to improve the management of patients with the different subtypes of VWD.

The distinction between quantitative (type 1) and qualitative (type 2) defects depends on the ability to recognize discrepancies among VWF assay results [82,93], as discussed in the section Diagnosis and Evaluation. Similarly, distinguishing between type 2A and type 2M VWD requires multimer gel analysis. Standards need to be established for using laboratory tests to make these important distinctions.

The example of Vicenza VWD illustrates some of these problems. Vicenza VWD was first described as a variant of VWD in which the level of plasma VWF is usually <15 IU dL⁻¹ and the VWF multimers are even larger than normal, like the ultralarge multimers characteristic of platelet VWF [94]. The low level of VWF in plasma in Vicenza VWD appears to be explained by the effect of a specific mutation, Arg1205His, that promotes clearance of VWF from the circulation about five times more rapidly than normal [43]. Because the newly synthesized multimers have less opportunity to be cleaved by ADAMTS13 before they are cleared, accelerated clearance alone may account for the increased multimer size in Vicenza VWD [95]. Whether Vicenza VWD is classified under type 1 VWD or type 2M VWD depends on the interpretation of laboratory test results. The abnormally large multimers and low RIPA values have led some investigators to prefer the designation of type 2M VWD [96]. However, the VWF:RCo/VWF:Ag ratio typically is normal, and large VWF multimers are not decreased relative to smaller multimers, so that other investigators have classified Vicenza VWD under type 1 VWD [43]. Regardless of how this variant is classified, the markedly shortened half-life of plasma VWF in Vicenza VWD is a key fact that, depending on the clinical circumstance, may dictate whether the patient should receive treatment with desmopressin or FVIII/VWF concentrates.

Type 1 VWD vs. low VWF: VWF level as a risk factor for bleeding

Persons who have very low VWF levels, i.e. <20 IU dL⁻¹, are likely to have VWF gene mutations, significant bleeding symptoms and a strongly positive family history [35,36,39,97–101]. Diagnosing type 1 VWD in these persons seems appropriate because they may benefit from changes in lifestyle and from specific treatments to prevent or control bleeding. Identification of affected family members may also be useful, and genetic counselling is simplified when the pattern of inheritance is straightforward.

In contrast, persons with VWF levels of 30–50 IU dL⁻¹, just below the usual normal range (50–200 IU dL⁻¹), pose problems for diagnosis and treatment. Among the total US population of approximately 300 million, VWF levels <50 IU dL⁻¹ are expected in about 7.5 million persons, who therefore would be at risk for a diagnosis of type 1 VWD. Because of the strong influence of ABO blood group on VWF level [45], about 80% of US residents...
who have low VWF have also blood type O. Furthermore, moderately low VWF levels and bleeding symptoms generally are not coinherited within families and are not strongly associated with intragenic VWF mutations [102–104]. In a recent Canadian study of 155 families who had type 1 VWD, the proportion showing linkage to the VWF locus was just 41% [100]. In a similar European study, linkage to the VWF locus depended on the severity of the phenotype. If plasma levels of VWF were <30 IU dL$^{-1}$, linkage was consistently observed, but if levels of VWF were higher than 30 IU dL$^{-1}$, the proportion of linkage was only 51% [99]. Furthermore, bleeding symptoms were not significantly linked to the VWF gene in these families [99].

Family studies suggest that 25–32% of the variance in plasma VWF is heritable [105,106]. Twin studies have reported greater heritability of 66–75% [107,108], although these values may be overestimates because of shared environmental factors [106,109]. Therefore, it appears that, at least in the healthy population, a substantial fraction of the variation in VWF level is not heritable.

Few genes have been identified that contribute to the limited heritability of VWF level. The major genetic influence on VWF level is the ABO blood group, which is thought to account for 20–30% of its heritable variance [14,108,110]. Therefore, it appears that, at least in the healthy population, a substantial fraction of the variation in VWF level is not heritable.

Table 6. Bleeding and VWF level in type 3 VWD heterozygotes.

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castaman et al. [399]</td>
<td>1 family with type 3 proband</td>
<td>11</td>
<td>None with bleeding; 6 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Eikenboom et al. [22]</td>
<td>8 families with type 3 probands</td>
<td>22</td>
<td>2 who had mild bleeding among 9 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Zhang et al. [400]</td>
<td>13 families with type 3 probands</td>
<td>55</td>
<td>22 who had mild bleeding among 38 with VWF &lt;50 IU dL$^{-1}$; 9 who had mild bleeding among 17 with VWF &gt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Schneppenheim et al. [113]</td>
<td>22 families with type 3 probands</td>
<td>44</td>
<td>5 who had epistaxis, bruising or menorrhagia among 24 with VWF &lt;50 IU dL$^{-1}$; 1 who had postoperative bleeding among 20 with VWF &gt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Eikenboom et al. [199]</td>
<td>1 family with type 3 proband</td>
<td>4</td>
<td>2 who had mild bleeding among 4 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Inbal et al. [401]</td>
<td>4 families with type 3 probands</td>
<td>20</td>
<td>None who had bleeding; 15 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Nichols et al. [402]</td>
<td>1 family with type 3 proband</td>
<td>6</td>
<td>None with bleeding; 2 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
<tr>
<td>Mannucci et al. [46]</td>
<td>15 families with type 3 probands</td>
<td>28</td>
<td>None who had bleeding; 19 with VWF &lt;50 IU dL$^{-1}$</td>
</tr>
</tbody>
</table>

VWD, von Willebrand disease; VWF, von Willebrand factor.

The attribution of bleeding to a low VWF level can be difficult because mild bleeding symptoms are very common, as discussed in the section Diagnosis and Evaluation, and the risk of bleeding is only modestly increased for persons who have moderately decreased VWF levels [47]. For example, in the course of investigating patients with type 3 VWD, approximately 190 obligate heterozygous relatives have had bleeding histories obtained and VWF levels measured (Table 6). The geometric mean VWF level was 47 IU dL$^{-1}$ [47], with a range (±2 SD) of 16–140 IU dL$^{-1}$. Among 117 persons who had VWF <50 IU dL$^{-1}$, 31 (26%) had bleeding symptoms. Among 74 persons who had VWF higher than 50 IU dL$^{-1}$, 10 (14%) had bleeding symptoms. Therefore, the relative risk of bleeding was 1.9 ($P = 0.046$, Fisher’s exact test) for persons who had low VWF. There was a trend for an increased frequency of bleeding symptoms at the lowest VWF

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Haemophilia (2008), 14, 171–232
levels: among 31 persons who had VWF levels <30 IU dL\(^{-1}\), 12 (39%) had symptoms. Bleeding was mild and consisted of epistaxis, bruising, menorrhagia and bleeding after tooth extraction. The one person who experienced postoperative bleeding had a VWF level higher than 50 IU dL\(^{-1}\) [113].

The management of bleeding associated with VWF deficiency would be facilitated by better understanding of the heritability of low VWF levels (in the range of 20–50 IU dL\(^{-1}\)), their association with intragenic VWF mutations, and their interactions with other modifiers of bleeding risk. Such data could provide a foundation for treating VWF level as a biomarker for a moderate risk of bleeding, much as high blood pressure and high cholesterol are treated as biomarkers for cardiovascular disease risk.

**Acquired von Willebrand syndrome**

Acquired von Willebrand syndrome (AVWS) refers to defects in VWF concentration, structure or function that are not inherited directly but are consequences of other medical disorders. Laboratory findings in AVWS are similar to those in VWD and may include decreased values for VWF:Ag, VWF:RCo or FVIII. The VWF multimer distribution may be normal, but the distribution often shows a decrease in large multimers similar to that seen in type 2A VWD [114,115]. AVWS usually is caused by one of three mechanisms: autoimmune clearance or inhibition of VWF, increased shear-induced proteolysis of VWF, or increased binding of VWF to platelets or other cell surfaces. Autoimmune mechanisms may cause AVWS in association with lymphoproliferative diseases, monoclonal gammapathies, systemic lupus erythematosus, other autoimmune disorders and some cancers. Autoantibodies to VWF have been detected in <20% of patients in whom they have been sought, suggesting that the methods for antibody detection may not be sufficiently sensitive or that AVWS in these settings may not always have an autoimmune basis.

Pathological increases in fluid shear stress can occur with cardiovascular lesions, such as ventricular septal defect and aortic stenosis, or with primary pulmonary hypertension. The increased shear stress can increase the proteolysis of VWF by ADAMTS13 enough to deplete large VWF multimers and thereby produce a bleeding diathesis that resembles type 2A VWD. The VWF multimer distribution improves if the underlying cardiovascular condition is treated successfully [114–119].

Increased binding to cell surfaces, particularly platelets, can also consume large VWF multimers. An inverse relationship exists between the platelet count and VWF multimer size, probably because increased encounters with platelets promote increased cleavage of VWF by ADAMTS13. This mechanism probably accounts for AVWS associated with myeloproliferative disorders; reduction of the platelet count can restore a normal VWF multimer distribution [120–122]. In rare instances, VWF has been reported to bind GPIb that was expressed ectopically on tumour cells [115,123].

Acquired von Willebrand syndrome has been described in hypothyroidism caused by non-immune mechanism [124]. Several drugs have been associated with AVWS; those most commonly reported include valproic acid, ciprofloxacin, griseofulvin and hydroxyethyl starch [114,115].

Acquired von Willebrand syndrome occurs in various conditions, but other clinical features may direct attention away from this potential cause of bleeding. More studies are needed to determine the incidence of AVWS and to define its contribution to bleeding in the many diseases and conditions with which it is associated.

**Prothrombotic clinical issues and VWF in persons who do not have VWD**

Whether elevation of VWF is prothrombotic has been the subject of several investigations. Both arterial and venous thrombotic disorders have been studied.

**Open heart surgery** Haemostatic activation after open heart surgery has been suggested as a mechanism of increased risk of postoperative thrombosis in this setting. A randomized trial comparing coronary artery surgery with or without cardiopulmonary bypass (‘off-pump’) found a consistent and equivalent rise in VWF:Ag levels at 1–4 postoperative days in the two groups [125], suggesting that the surgery itself, rather than cardiopulmonary bypass, was responsible for the rise in VWF. There is no direct evidence that the postoperative rise in VWF contributes to the risk of thrombosis after cardiac surgery.

**Coronary artery disease** Three large prospective studies of subjects without evidence of ischaemic heart disease at entry have shown, by univariate analysis, a significant association of VWF:Ag level at entry with subsequent ischaemic coronary events [126–128]. However, the association remained significant by multivariate analysis in only one subset of subjects in these studies [126], a finding that could
have occurred by chance. These findings suggest that the association of VWF with the incidence of coronary ischaemic events is relatively weak and may not be directly causal.

Thrombosis associated with atrial fibrillation A prospective study of vascular events in subjects with atrial fibrillation found, by univariate analysis, a significant association of VWF:Ag level with subsequent stroke or vascular events. The association with vascular events remained significant with multivariate analysis [129].

Thrombotic thrombocytopenic purpura The hereditary deficiency or acquired inhibition of a VWF-cleaving protease, ADAMTS13, is associated with the survival in plasma of ultralarge VWF multimers, which are involved in the propensity to development of platelet-rich thrombi in the microvasculature of individuals who have TTP [130,131].

Deep vein thrombosis In a case–control study of 301 patients, evaluated at least 3 months after cessation of anticoagulation treatment for a first episode of deep vein thrombosis (DVT), plasma levels of VWF:Ag and FVIII activity were related to risk of DVT, according to univariate analysis. In multivariate analysis, the relation of VWF level with risk of DVT was not significant after adjustment for FVIII levels [132].

Diagnosis and evaluation

Introduction

The evaluation of a person for possible VWD or other bleeding disorders may be initiated because of various clinical indications (Fig. 3). These indications and situations may include evaluation of (i) an asymptomatic person who will undergo a surgical or interventional procedure; (ii) persons who present with current symptoms of or a history of increased bleeding, abnormal laboratory studies, a positive family history of a bleeding disorder or a combination of these factors; or (iii) persons who present with a prior diagnosis of VWD but do not have supporting laboratory documentation. In all cases, the initial step in assessment should focus on key aspects of the person’s clinical history to determine whether the person may benefit from further diagnostic evaluation. This section is divided into two parts. The first part uses a summary of the medical literature to suggest questions for an initial assessment of persons presenting with concerns about bleeding issues or for evaluation before procedures that may increase their risk of bleeding. Using the answers to the initial assessment, the second part focuses on a strategy for optimal laboratory assessment of persons who potentially have bleeding disorders and suggests guidelines for interpretation of laboratory results.

Evaluation of the patient

History, signs and symptoms The initial clinical assessment of a person who is being evaluated for VWD should focus on a personal history of excessive bleeding throughout the person’s life and any family history of a bleeding disorder. The history of bleeding should identify the spontaneity and severity, sites of bleeding, duration of bleeding, type of insult or injury associated with bleeding, ease with which bleeding can be stopped and concurrent medications — such as aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel (Plavix), warfarin or heparin — at the onset of bleeding. Particularly when an invasive procedure is anticipated, the person should be asked whether he or she is currently taking any of these medications and also whether he or she has any history of liver or kidney disease, blood or bone marrow disease or high or low-platelet counts. If a history of any of these disorders is present, further appropriate evaluation or referral should be undertaken.

Clinical manifestations The most common presenting symptoms in persons who receive a diagnosis of VWD are summarized in Table 7. Symptoms usually involve mucous membranes and skin sites, and bleeding is of mild-to-moderate severity (bleeding that does not require blood transfusions and usually does not require visits to the physician) for most persons with VWD, reflecting the predominance of type 1 VWD. However, life-threatening bleeding (central nervous system and gastrointestinal tract) can occur in persons with type 3 VWD, in some persons with type 2 VWD, and rarely in persons with type 1 VWD. Uncommon bleeding manifestations, such as haemarthrosis, are more common in persons who have a more severe deficiency, especially those with type 3 VWD [87,133]. Clinical symptoms may also be modified by coexisting illnesses or other medications. For example, use of aspirin or NSAIDs can exacerbate the bleeding tendency, whereas use of oral contraceptives can decrease bleeding in women with VWD.

The clinical evaluation of bleeding symptoms is a challenge, because mild bleeding symptoms are also
common in healthy populations (Table 7, ‘Normals’ column). Responses to questionnaires used to survey healthy controls indicate that they identify themselves as having specific bleeding manifestations as frequently as persons with VWD, particularly type 1 VWD (Table 7) [134–137]. In addition, a family history of bleeding was reported in 44% of healthy children undergoing tonsillectomy [137] and by 35% [135] or 60% [138] of persons referred because of bleeding. Because bleeding symptoms are so prevalent, it may be impossible to establish a causal relationship between bleeding and low VWF.

Some of the most important clinical issues in VWD apply specifically to women, particularly menorrhagia. Studies of women with VWD report a high prevalence of menorrhagia (Table 7), although the definition of menorrhagia is not clearly specified in most of these studies and the diagnostic criteria for VWD are not uniform. The sensitivity of menorrhagia as a predictor of VWD may be estimated as 32–100%. However, menorrhagia is a common symptom, occurring with a similar frequency in healthy controls and women with VWD; therefore, it is not a specific marker for VWD (Table 7). In a survey of 102 women who had VWD and were registered at haemophilia treatment centres in the United States, 95% reported a history of menorrhagia, but 61% of controls also reported a history of menorrhagia [139]. Studies have reported a prevalence of VWD of between 5% and 20% among women who have menorrhagia [140–146]. Therefore, the specificity of menorrhagia as a predictor of
VWD can be estimated as 5–20%. Three findings that predict abnormal menstrual blood loss of more than 80 mL are (i) clots larger than approximately 1 inch in diameter; (ii) low serum ferritin and (iii) the need to change a pad or tampon more than hourly [147].

Further evaluation for inherited bleeding disorders

Because ‘bleeding symptoms’ other than menorrhagia are reported frequently by persons who have apparently normal haemostasis, it is important to ask questions that can best identify persons who have a true bleeding disorder. Sramek and colleagues [135] used a written questionnaire with patients who had a proven bleeding disorder. When the responses were compared with those of a group of healthy volunteers, the most informative questions were related to (i) prolonged bleeding after surgery, including after dental extractions and (ii) identification of family members who have an established bleeding disorder (Table 8, columns 2–5). A history of muscle or joint bleeding (haematomas or haemarthroses) may also be helpful when associated with the above symptoms.

General questions that relate to isolated bleeding symptoms — such as frequent gingival bleeding, profuse menstrual blood loss, bleeding after delivery and epistaxis in the absence of other bleeding symptoms — were not informative [135]. The study also found that an elaborate interview after referral to a haematologist was not particularly helpful when attempting to distinguish persons who have a true bleeding disorder from persons who have a ‘suspected’ bleeding disorder, implying that the selection of those with bleeding disorders had already been made by the referring doctor [135].

Drews et al. [148] attempted to develop a questionnaire-based screening tool to identify women who might benefit from a diagnostic work-up for VWD. They conducted a telephone survey of 102 women who had a diagnosis of type 1 VWD and were treated at a haemophilia treatment centre; 88 of their friends served as controls. With the exception of postpartum transfusions, all study variables were reported more frequently by women who had VWD than by their friends (Table 8, columns 6 and 7). In addition, positive responses to multiple questions were more likely to be obtained from patients who have an inherited bleeding disorder [148]. An important limitation of this study is that these women were more symptomatic than most women who have a diagnosis of type 1 VWD, indicating a more severe phenotype of the disease; this fact might decrease the sensitivity of the questions in persons who have milder type 1 VWD and fewer symptoms.

More recently, Rodeghiero and colleagues [149] compared responses to a standardized questionnaire obtained from 42 obligatory carriers of VWD (from well-characterized families) to responses from 215 controls. The questionnaire covered 10 common bleeding symptoms (including all symptoms in Table 7 and postpartum haemorrhage), with assigned scores for each ranging from 0 (no symptoms) to 3 (severe symptoms, usually including hospitalization, transfusion support or both). With this instrument, the researchers found that having a cumulative total bleeding score of 3 in men or 5 in

### Table 7. Common bleeding symptoms of healthy individuals and patients with VWD.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Normals ($n = 500$)</th>
<th>All types of VWD ($n = 264$)</th>
<th>Type 1 VWD ($n = 42$)</th>
<th>Type 2 VWD ($n = 497$)</th>
<th>Type 3 VWD ($n = 385$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>4.6–22.7</td>
<td>38.1–62.5</td>
<td>53–61</td>
<td>63</td>
<td>66–77</td>
</tr>
<tr>
<td>Menorrhagia§</td>
<td>23–68.4</td>
<td>47–60</td>
<td>32</td>
<td>32</td>
<td>56–69</td>
</tr>
<tr>
<td>Bleeding after dental extraction</td>
<td>4.8–41.9</td>
<td>28.6–51.5</td>
<td>17–31</td>
<td>39</td>
<td>53–70</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>11.8–50</td>
<td>49.2–50.4</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bleeding from minor cuts or abrasions</td>
<td>0.2–33.3</td>
<td>36</td>
<td>36</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>7.4–47.1</td>
<td>26.1–34.8</td>
<td>29–31</td>
<td>35</td>
<td>56</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>1.4–28.2</td>
<td>19.5–28</td>
<td>20–47</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>0–14.9</td>
<td>6.3–8.3</td>
<td>2–3</td>
<td>4</td>
<td>37–45</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.6–27.7</td>
<td>14</td>
<td>5</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

NR, not reported; VWD, von Willebrand disease.

* A total of 341 individuals were sent a questionnaire, but the precise number responding was not provided.

† Study included women only.

‡ Study included males only.

§ Calculated for females older than 13–15 years.
women was very specific (98.6%) but not as sensitive (69.1%) for type 1 VWD. Limitations of this study include its retrospective design and awareness of the respondent’s diagnosis by the person administering the questionnaire. This questionnaire is available online [149].

A similar retrospective case–control study [150] used a standardized questionnaire like that of Rodeghiero et al. [149] to compare bleeding symptoms of 144 index cases who had type 1 VWD with those in 273 affected relatives, 295 unaffected relatives and 195 healthy controls. The interviewers were not blinded to subject’s status. At least one bleeding symptom was reported by approximately 98% of index cases, 89% of affected relatives, 32% of unaffected relatives and 12% of healthy controls. The major symptoms of affected persons (excluding index cases) included bleeding after tooth extraction, nosebleeds, menorrhagia, bleeding into the skin, postoperative bleeding and bleeding from minor wounds. Using a bleeding score calculated from the data for comparison, the severity of bleeding diminished with increasing plasma VWF, not only for subjects who had low VWF levels, but throughout the normal range as well. Although the mean bleeding score was significantly different among several groups, the distribution was sufficiently broad that the bleeding score could not predict the affected or unaffected status of individuals.

In a related study, bleeding symptoms were assessed with the same questionnaire in 70 persons who were obligatory carriers of type 3 VWD, 42 persons who were obligate carriers of type 1 VWD (meaning affected family members of index cases who had type 1 VWD) and 215 persons who were healthy controls [151]. Carriers of type 3 VWD were compared with carriers of type 1 VWD to address the question of whether the distinct types of VWF mutations associated with these conditions predisposed to the same or different severity of bleeding. Approximately 40% of carriers of type 3 VWD, 82% of carriers of type 1 VWD and 23% of healthy

### Table 8. Prevalences of characteristics in patients with diagnosed bleeding disorders vs. healthy controls.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Univariate analysis*</th>
<th>Multivariate analysis*</th>
<th>Women who have VWD†</th>
<th>Type 1 VWD families‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members have an established bleeding disorder</td>
<td>97.5 38.3–248</td>
<td>50.5 12.5–202.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Profuse bleeding from small wounds</td>
<td>67.2 28.4–159</td>
<td>30.0 8.1–111.1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Profuse bleeding at site of tonsillectomy/adenoidecotomy</td>
<td>27.7 8.0–96.1</td>
<td>11.5 1.2–111.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>12.7 8.0–20.2</td>
<td>9.9 3.0–32.3</td>
<td>9.8</td>
<td>4.8–17.3</td>
</tr>
<tr>
<td>Profuse bleeding after surgery</td>
<td>23.0 10.6–50.1</td>
<td>5.8 1.3–26.4</td>
<td>52.9</td>
<td>42.8–62.9</td>
</tr>
<tr>
<td>Muscle bleeding (ever)</td>
<td>13.3 6.4–27.7</td>
<td>4.8 0.7–31.4</td>
<td>9.8</td>
<td>4.8–17.3</td>
</tr>
<tr>
<td>Frequent nosebleeds</td>
<td>3.5 2.0–6.2</td>
<td>3.8 0.9–15.7</td>
<td>61.8</td>
<td>51.6–71.2</td>
</tr>
<tr>
<td>Profuse bleeding at site of dental extraction</td>
<td>39.4 20.6–75.5</td>
<td>3.2 0.9–11.3</td>
<td>54.9</td>
<td>44.7–64.8</td>
</tr>
<tr>
<td>Blood in stool (ever)</td>
<td>2.8 1.7–4.6</td>
<td>2.8 0.7–11.7</td>
<td>13.7</td>
<td>7.7–22.0</td>
</tr>
<tr>
<td>Family members with bleeding symptoms</td>
<td>28.6 15.0–54.6</td>
<td>2.5 0.7–9.4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Joint bleeding (ever)</td>
<td>8.6 4.8–15.2</td>
<td>2.5 0.6–10.2</td>
<td>20.6</td>
<td>13.2–29.7</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>5.4 3.0–9.8</td>
<td>2.5 0.6–9.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Haemorrhage at time of delivery</td>
<td>5.3 2.3–12.0</td>
<td>2.1 0.3–13.5</td>
<td>50.0</td>
<td>39.9–60.1</td>
</tr>
<tr>
<td>Frequent gingival bleeding</td>
<td>2.8 1.9–4.2</td>
<td>0.7 0.3–2.0</td>
<td>76.5</td>
<td>67.0–84.3</td>
</tr>
<tr>
<td>Haematuria (ever)</td>
<td>3.2 1.8–5.6</td>
<td>0.5 0.1–2.3</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; VWD, von Willebrand disease.
Ellipses indicate data were not reported.

*Univariate and multivariate analyses from Sramek et al. [135] comparing 222 patients who had a known bleeding disorder (43% mild VWD) and 341 healthy volunteers.
†Compiled from responses to a questionnaire sent to 102 women, who had type 1 VWD, in a haemophilia treatment centre, from Drews et al. [148].
‡Compiled from interviews comparing affected and unaffected family members of patients who had type 1 VWD, from Tosetto et al. [150] and F. Rodeghiero (personal communication). The index cases (patients who had VWD) were not included in the analysis.
controls had at least one bleeding symptom. The major bleeding symptoms in carriers of type 3 VWD were bleeding into skin and postsurgical bleeding. The results suggest that carriers of type 3 VWD are somewhat distinct, because they have bleeding symptoms more frequently than healthy controls but less frequently than persons who have or are carriers of type 1 VWD. Usually, carriers of type 1 VWD have lower VWF levels than carriers of type 3 VWD.

**Family history** Although a family history that is positive for an established bleeding disorder is useful in identifying persons who are likely to have VWD, such a history is frequently not present. This is most commonly the case for persons with milder forms of VWD and whose family members may have minimal, if any, symptoms. As shown in Table 8, the presence of a documented bleeding disorder in a family member is extremely helpful in deciding which persons to evaluate further, whereas a family history of bleeding symptoms is less helpful.

**Summary of medical history evaluation** Table 9 summarizes suggested questions that can be used to identify persons who should be considered for further evaluation for VWD with laboratory studies.

**Physical examination** The physical examination should be directed to confirm evidence for a bleeding disorder, including size, location and distribution of ecchymoses (e.g. truncal), haematomas, petechiae and other evidence of recent bleeding. The examination should also focus on findings that may suggest other causes of increased bleeding, such as evidence of liver disease (e.g. jaundice), splenomegaly, arthropathy, joint and skin laxity (e.g. Ehlers-Danlos syndrome), telangiectasia (e.g. hereditary haemorrhagic telangiectasia), signs of anaemia or anatomic lesions on gynaecological examination.

**Acquired von Willebrand Syndrome** Persons with AVWS present with bleeding symptoms similar to those described above, except that the past personal history and family history are negative for bleeding symptoms. AVWS may occur spontaneously or in association with other diseases, such as monoclonal gammapathies, other plasma cell dyscrasias, lymphoproliferative diseases, myeloproliferative disorders (e.g. essential thrombocythemia), autoimmune disorders, valvular and congenital heart disease, certain tumours and hypothyroidism [114,152]. The evaluation should be tailored to finding conditions associated with AVWS.

<table>
<thead>
<tr>
<th>Table 9. Suggested questions for screening persons for a bleeding disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Questions</strong></td>
</tr>
<tr>
<td>1. Have you or a blood relative ever needed medical attention for a bleeding problem, or have you been told you have a bleeding disorder or problem?</td>
</tr>
<tr>
<td>2. During or after surgery?</td>
</tr>
<tr>
<td>3. With dental procedures or extractions?</td>
</tr>
<tr>
<td>4. With trauma?</td>
</tr>
<tr>
<td>5. During childbirth or for heavy menses?</td>
</tr>
<tr>
<td>6. Ever had bruises with lumps?</td>
</tr>
<tr>
<td>7. Do you have or have you ever had Liver or kidney disease?</td>
</tr>
<tr>
<td>8. A blood or bone marrow disorder?</td>
</tr>
<tr>
<td>9. A high- or low-platelet count?</td>
</tr>
</tbody>
</table>

| **Additional Questions** |
| 1. Have you or a blood relative who has a bleeding disorder, such as von Willebrand disease or haemophilia? |
| 2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 min or recurring spontaneously during the 7 days after the wound? |
| 3. Have you ever had heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy? |
| 4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise? |
| 5. Have you ever had a spontaneous nosebleed that required more than 10 min to stop or needed medical attention? |
| 6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention? |
| 7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach or a polyp in the colon), that required medical attention? |
| 8. Have you ever had anaemia requiring treatment or received a blood transfusion? |
| 9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter or changing a pad or tampon more than hourly or by resulting in anaemia or low iron level? |

NSAIDs, non-steroidal anti-inflammatory drugs.

*Initial questions, such as for an asymptomatic person who will undergo a surgical or interventional procedure.

†Additional questions such as for persons answering positively to the initial questions or for persons presenting with specific issues, including (i) current bleeding symptoms or a history of increased bleeding; (ii) abnormal laboratory test results; (iii) family history of a bleeding disorder; or (iv) previous diagnosis of a bleeding disorder, including von Willebrand disease. The initial questions should also be asked, if not already done.

Sources: Laffan et al. [8], Drews et al. [148] and Dean et al. [158].
Laboratory diagnosis and monitoring

An algorithm for using clinical laboratory studies to make the diagnosis of VWD is summarized in Fig. 4.

Ideally, a simple, single laboratory test could screen for the presence of VWD. Such a screening test would need to be sensitive to the presence of most types of VWD and would have a low false-positive rate. However, no such test is available. In the past, the activated partial thromboplastin time (PTT) and BT were recommended as diagnostic tests. These tests were probably satisfactory for detecting severe type 3 VWD, but as variant VWD and milder forms of VWD were characterized, it became apparent that many of the persons who have these conditions had normal PTT and BT results.

Initial haemostasis laboratory evaluation

An initial haemostasis laboratory evaluation usually includes (i) a platelet count and complete blood cell count; (ii) PTT; (iii) prothrombin time; and (iv) optionally either a fibrinogen level or a thrombin time (Fig. 4). This testing neither rules in nor rules out VWD, but it can suggest whether coagulation factor deficiency or thrombocytopenia might be the potential cause of clinical bleeding. If the mucocutaneous bleeding history is strong, initial VWD assays (VWF:Ag, VWF:RCo and FVIII) should be considered at the first visit.

Some centres add a BT or a platelet function analyzer (PFA-100) assay to their initial laboratory tests. The BT test is a non-specific test and subject to operational variation. It has been argued that the BT test is a population-based test that was never intended to test individuals [153]. Variables that may affect results include a crying or wiggling child, differences in the application of the blood pressure cuff, and the location, direction and depth of the cut made by the device. This test also has a potential for causing keloid formation and scarring, particularly in non-White individuals.

The PFA-100 test result has been demonstrated to be abnormal in the majority of persons with VWD, other than those with type 2N, but its use for population screening for VWD has not been established [154–157]. Persons with severe type 1 VWD or type 3 VWD usually have abnormal PFA-100 values, whereas persons with mild or moderate type 1 VWD and some with type 2 VWD may not have abnormal results [158–160]. When persons are studied by using both the BT and PFA-100, the results are not always concordant [157,159,161].

When using the PTT in the diagnosis of VWD, results of this test are abnormal only if the FVIII is sufficiently reduced. Because the FVIII gene is normal...
in VWD, the FVIII deficiency is secondary to the deficiency of VWF, its carrier protein. In normal individuals, the levels of FVIII and VWF:RCo are approximately equal, with both averaging 100 IU dL\(^{-1}\). In type 3 VWD, the plasma FVIII level is usually <10 IU dL\(^{-1}\) and represents the steady state of FVIII in the absence of its carrier protein. In persons with type 1 VWD, the FVIII level is often slightly higher than the VWF level and may fall within the normal range. In persons with type 2 VWD (except for type 2N VWD in which it is decreased), the FVIII is often two to three times higher than the VWF activity (VWF:RCo) [162,163]. Therefore, the PTT is often within the normal range. If VWF clearance is the cause of low VWF, the FVIII reduction parallels that of VWF, probably because both proteins are cleared together as a complex.

**Initial tests for VWD** The initial tests commonly used to detect VWD or low VWF are determinations of plasma levels of (i) VWF:Ag; (ii) VWF:RCo; and (iii) FVIII (Fig. 4). These three tests, readily available in most larger hospitals, measure the amount of VWF protein present in plasma (VWF:Ag), the function of the VWF protein that is present as VWF:RCo, and the ability of the VWF to serve as the carrier protein to maintain normal FVIII survival. If any of the above tests is abnormally low, the next steps should be discussed with a coagulation specialist, who may recommend referral to a specialized centre and repeating the initial VWD laboratory tests in addition to performing other tests.

**VWF:Ag assay.** VWF:Ag is an immunoassay that measures the concentration of VWF protein in plasma. Commonly used methods are based on enzyme-linked immunosorbent assay (ELISA) or automated latex immunoassay (LIA). As discussed below, the standard reference plasma is critical and should be keyed to the World Health Organization (WHO) standard. The person’s test results should be reported in international units (IU), either as international units per decilitre (IU dL\(^{-1}\)) or as international units per millilitre (IU mL\(^{-1}\)). Most laboratories choose IU mL\(^{-1}\), because it is similar to the conventional manner of reporting clotting factor assays as a percentage of normal.

**VWF:RCo assay.** VWF:RCo is a functional assay of VWF that measures its ability to interact with normal platelets. The antibiotic ristocetin causes VWF to bind to platelets, resulting in platelet clumps and their removal from the circulation. Ristocetin was removed from clinical trials because it caused thrombocytopenia. This interaction was developed into a laboratory test that is still the most widely accepted functional test for VWF. (In vivo, however, it is the high shear in the microcirculation, and not a ristocetin-like molecule, that causes the structural changes in VWF that lead to VWF binding to platelets.)

Several methods are used to assess the platelet agglutination and aggregation that result from the binding of VWF to platelet GPIb induced by ristocetin (VWF:RCo). The methods include (1) time to visible platelet clumping using ristocetin, washed normal platelets (fresh or formalinized) and dilutions of patient plasma; (2) slope of aggregation during platelet aggregometry using ristocetin, washed normal platelets and dilutions of the person’s plasma; (3) automated turbidometric tests that detect platelet clumping, using the same reagents noted above; (4) ELISAs that assess direct binding of the person’s plasma VWF to platelet GPIb (the GPIb may be derived from plasma glycoalycin) in the presence of ristocetin [164–166] and (5) the binding of a monoclonal antibody to a conformation epitope of the VWF A1 loop [167]. Method (5) can be performed in an ELISA or LIA format. It is not based on ristocetin binding. The first three assays above may use platelet membrane fragments containing GPIb rather than whole platelets. The sensitivity varies for each laboratory and each assay; in general, however, methods 1 and 2, which measure platelet clumping by using several dilutions of the person’s plasma, are quantitative to approximately 6–12 IU dL\(^{-1}\) levels. Method 3 is quantitative to about 10–20 IU dL\(^{-1}\). Method 4 can measure VWF:RCo to <1 IU dL\(^{-1}\), and a variation of it can detect the increased VWF binding to GPIb seen in type 2B VWD [168]. Some automated methods are less sensitive and require modification of the assay to detect levels <10 IU dL\(^{-1}\). Each laboratory should define the linearity and limits of its assay. Several monoclonal ELISAs (method 5) that use antibodies directed to the VWF epitope containing the GPIb-binding site have been debated because the increased function of the largest VWF multimers is not directly assessed [169].

The VWF:RCo assay has high intralaboratory and interlaboratory variation, and it does not actually measure physiological function. The coefficient of variation (CV) has been measured in laboratory surveys at 30% or greater, and the CV is still higher when the VWF:RCo is lower than 12–15 IU dL\(^{-1}\) [170–174]. This becomes important not only for the initial diagnosis of VWD, but also for determining whether the patient has type 1 vs. type 2 VWD (see additional discussion in the section below, Ratio of VWF:RCo to VWF:Ag). Despite these limitations, it
is still the most widely accepted laboratory measure of VWF function. Results for VWF:RCo should be expressed in IU dL$^{-1}$ on the basis of the WHO plasma standard.

**FVIII assay.** FVIII coagulant assay is a measure of the cofactor function of the clotting factor, FVIII, in plasma. In the context of VWD, FVIII activity measures the ability of VWF to bind and maintain the level of FVIII in the circulation. In the United States, the assay is usually performed as a 1-stage clotting assay based on the PTT, although some laboratories use a chromogenic assay. The clotting assay, commonly done using an automated or semiautomated instrument, measures the ability of plasma FVIII to shorten the clotting time of FVIII-deficient plasma. Because this test is important in the diagnosis of haemophilia, the efforts to standardize this assay have been greater than those applied to other haemostasis assays. FVIII activity is labile, with the potential for spuriously low assay results if blood specimen collection, transport or processing is suboptimal. Like the tests discussed above, it should be expressed in IU dL$^{-1}$ on the basis of the WHO plasma standard.

**Laboratory results in different VWD subtypes** Expected patterns of laboratory results in different subtypes of VWD, depicted in Fig. 5, include results of the three initial VWD tests (VWF:Ag, VWF:RCo and FVIII) and results of other assays for defining and classifying VWD subtypes. The three initial tests (or at least the VWF:RCo and FVIII assays) are also used for monitoring therapy.

**Other assays to measure VWF, define and diagnose VWD and classify subtypes**

**VWF multimer analysis.** The VWF multimer test, an assay that is available in some larger centres and in commercial laboratories, is usually performed after

![VWF multimer pattern](image)

Fig. 5. Expected laboratory values in von Willebrand disease (VWD). The symbols and values represent prototypical cases. In practice, laboratory studies in certain patients may deviate slightly from these expectations. L, 30–50 IU dL$^{-1}$; ↓, ↓↓, ↓↓↓, relative decrease; ↑, ↑↑, ↑↑↑, relative increase; BT, bleeding time; FVIII, factor VIII activity; GPIb, platelet glycoprotein Ib complex; LD-RIPA, low-dose ristocetin-induced platelet aggregation (concentration of ristocetin ≤0.6 mg mL$^{-1}$); N, normal; PFA-100-CT, platelet function analyzer closure time; PLT-VWD, platelet-type VWD; RIPA, ristocetin-induced platelet aggregation; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity. (Courtesy of R. R. Montgomery, the BloodCenter of Wisconsin and Medical College of Wisconsin, Milwaukee, Wisconsin; adapted from and used with permission.) *Persons with PLT-VWD have a defect in their platelet GPIb. Laboratory test results resemble type 2B VWD, and both have a defect in their LD-RIPA. In the VWF platelet-binding assay, persons with type 2B VWD have abnormally increased platelet binding. Normal persons and those with PLT-VWD have no binding of their VWF to normal platelets at low ristocetin concentrations.

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the initial VWD testing indicates an abnormality, preferably using a previously unthawed portion of the same sample or in association with a repeated VWD test panel (VWF:Ag, VWF:RCo and FVIII) using a fresh plasma sample. VWF multimer analysis is a qualitative assay that depicts the variable concentrations of the different-sized VWF multimers by using sodium dodecyl sulphate–protein electrophoresis followed by detection of the VWF multimers in the gel, using a radiolabelled polyclonal antibody or a combination of monoclonal antibodies. Alternatively, the protein is transferred to a membrane (Western blot), and the multimers are identified by immunofluorescence or other staining techniques [101,175,176].

Multimer assays are designated as ‘low resolution’ (which differentiate the largest multimers from the intermediate and small multimers) or ‘high resolution’ (which differentiate each multimer band of the smaller multimers into 3–8 satellite bands). For diagnostic purposes, the low-resolution gel systems are used primarily; these systems help to differentiate the type 2 VWD variants from types 1 or 3 VWD. Figure 6 illustrates the differences between these two techniques with regard to the resolution of high- and low-molecular-weight multimers. It should be noted that multimer appearance alone does not define the variant subtype and that only types 2A, 2B and platelet-type VWD (PLT-VWD) have abnormal multimer distributions with relative deficiency of the largest multimers. An exception is Vicenza variant VWD with ultralarge VWF multimers and low VWF. For more information about VWF multimer findings in type 2 VWD variants, see

![Multimer analysis diagram](Image)

**Fig. 6.** Analysis of von Willebrand factor (VWF) multimers. The distribution of VWF multimers can be analysed using sodium dodecyl sulphate (SDS)–agarose electrophoresis followed by immunostaining. Low-resolution gels (0.65% agarose, left side) can demonstrate the change in multimer distribution of the larger multimers (top of the gel), while high-resolution gels (2–3% agarose, right side) can separate each multimer into several bands that may be distinctive. For example, the lowest band in the 0.65% gel can be resolved into five bands in the 3% agarose gel, but the 3% gel fails to demonstrate the loss of high-molecular-weight multimers seen at the top in the 0.65% gel. The dotted line indicates the resolution of the smallest band into several bands in the 3% agarose gel. In each gel, normal plasma (NP) is run as a control. Type 1 von Willebrand disease (VWD) plasma has all sizes of multimers, but they are reduced in concentration. Type 2A VWD plasma is missing the largest and intermediate multimers, while type 2B VWD plasma is usually missing just the largest VWF multimers. No multimers are identified in type 3 VWD plasma. Patients with thrombotic thrombocytopenic purpura (TTP) may have larger than normal multimers when studied with low-resolution gels. (Courtesy of R. R. Montgomery, the BloodCenter of Wisconsin and Medical College of Wisconsin, Milwaukee, Wisconsin; used with permission).
the section above (Type 2 VWD) and associated references.

**Low-dose RIPA.** RIPA and the VWF platelet-binding (VWF:PB) assay are two tests that are performed to aid in diagnosing type 2B VWD. RIPA may be done as part of routine platelet aggregation testing. Low-dose RIPA is carried out in platelet-rich plasma, using a low concentration of ristocetin (usually <0.6 mg mL\(^{-1}\), although ristocetin lots vary, resulting in the use of slightly different ristocetin concentrations). This low concentration of ristocetin does not cause VWF binding and aggregation of platelets in samples from normal persons, but it does cause VWF binding and aggregation of platelets in samples from patients with either type 2B VWD or mutations in the platelet VWF receptor. The latter defects have been termed pseudo-VWD or PLT-VWD, and they can be differentiated from type 2B VWD by VWF:PB assay. At higher concentrations of ristocetin (1.1–1.3 mg mL\(^{-1}\)), RIPA is reduced in persons with type 3 VWD. However, the test is not sufficiently sensitive to reliably diagnose other types of VWD.

**VWF:PB assay.** The VWF:PB assay measures the binding of VWF to normal paraformaldehyde-fixed platelets using low concentrations of ristocetin (usually 0.3–0.6 mg mL\(^{-1}\)) [177]. The amount of VWF bound to the fixed platelets is determined by using a labelled antibody. Clinically normal individuals or those with types 1, 2A, 2M, 2N and 3 VWD exhibit minimal or no binding to platelets at the concentration of ristocetin used, but patients with type 2B VWD exhibit extensive binding that causes their variant phenotype (a loss of high-molecular-weight multimers, decreased ristocetin cofactor activity, and thrombocytopenia). Both type 2B VWD and PLT-VWD have agglutination of platelet-rich plasma to low-dose ristocetin, but the VWF:PB assay can differentiate type 2B VWD from PLT-VWD. Only VWF from persons with type 2B VWD has increased VWF:PB, while VWF from persons with PLT-VWD has normal VWF:PB with low doses of ristocetin.

**VWF collagen-binding assay.** The VWF collagen-binding (VWF:CB) assay measures binding of VWF to collagen. The primary site of fibrillar collagen binding is in the A3 domain of VWF. Like the ristocetin cofactor assay, the VWF:CB assay is dependent on VWF multimeric size, with the largest multimers binding more avidly than the smaller forms. The VWF:CB assay performance and sensitivity to VWD detection or discrimination among VWD subtypes is highly dependent on the source of collagen, as well as on whether type 1 collagen or a mixture of type 1/3 collagen is used [178,179]. Only a few patients have been identified who have specific collagen-binding defects that are independent of multimer size, and the defects have been associated with a mutation of VWF in the A3 domain [75]. The prevalence of such defects is unknown. The place of VWF:CB in the evaluation of VWD has not been established. In principle, however, patients who have defects in collagen binding may have a normal VWF:RCo and thus escape clinical diagnosis unless a VWF:CB assay is performed. Limited studies suggest that supplementary VWF:CB testing, complementing assays of VWF:RCo and VWF:Ag, can improve the differentiation of type 1 VWD from types 2A, 2B or 2M VWD [170,180,181].

**VWF FVIII-binding assay.** The VWF FVIII-binding (VWF:FVIIIb) assay measures the ability of a person’s VWF to bind added exogenous FVIII and is used to diagnose type 2N VWD [77,79,80,182,183]. The assay is performed by capturing the person’s VWF on an ELISA plate, removing the bound endogenous FVIII, and then adding back a defined concentration of exogenous recombinant FVIII. The amount of FVIII bound is determined by chromogenic or immunological FVIII assay. The level of this bound FVIII is then related to the amount of the person’s VWF initially bound in the same well. In clinical experience, type 2N VWD is usually recessive; the person is either homozygous or compound heterozygous (one allele is type 2N and the other is a type 1 or null allele). In either case, the VWF in the circulation does not bind FVIII normally, and the concentration of FVIII is thus decreased.

**Ratio of VWF:RCo to VWF:Ag.** The VWF:RCo/VWF:Ag ratio can aid in the diagnosis of types 2A, 2B and 2M VWD and help differentiate them from type 1 VWD. For example, a VWF:RCo/VWF:Ag ratio of <0.6 [184] or 0.7 has been used as a criterion for dysfunctional VWF [8,185]. A similar approach has been proposed for the use of the VWF:CB/VWF:Ag ratio [8,185]. In type 2A VWD, the ratio is usually low, and in type 2B VWD, the VWF:RCo/VWF:Ag ratio is usually low but may be normal. In type 2M VWD, the VWF:Ag concentration may be reduced or normal, but the VWF:RCo/VWF:Ag ratio is <0.7. One study [72] determined the VWF:RCo/VWF:Ag ratio in nearly 600 individuals with VWF levels lower than 55 IU dL\(^{-1}\) who had normal VWF multimers. The study used this ratio to identify families who had type 2 VWD, but most centres do not have the ability to establish normal ranges for patients who have low VWF. Additionally, the VWF:RCo assay has a CV as high as 30% or more, depending on the methods used, whereas the CV for the VWF:Ag assay is somewhat lower. The high
intrinsinc variability of the VWF:RCo assay, especially at low levels of VWF, can make the VWF:RCo/VWF:Ag ratio an unreliable criterion for the diagnosis of type 2 VWD [170,172–174].

It is important that the same plasma standard used in both the VWF:RCo and VWF:Ag assays and that a reference range for the VWF:RCo/VWF:Ag ratio and its sensitivity to types 2A and 2M VWD be determined in each laboratory. Because no large multicentre studies have evaluated the precise ratio that should be considered abnormal, a ratio in the range of less than 0.5–0.7 should raise the suspicion of types 2A, 2B or 2M VWD. Further confirmation should be sought by additional testing (eg. repeated VWD test panel and VWF multimer study or sequencing of the A1 region of the VWF gene) [186]. Subsequent sections provide more information about the VWF:RCo/VWF:Ag ratio (Diagnostic Recommendations II.C.1.a and III.B and Evidence Table 3 [10]).

ABO blood type. ABO blood types have a notable effect on plasma VWF (and FVIII) concentrations [45,187]. Individuals who have blood type O have concentrations approximately 25% lower than persons who have other ABO blood types. The diagnosis of type 1 VWD occurs more frequently in individuals who have blood group type O [45]. Table 10 illustrates the effect of blood type on VWF:Ag level.

Although stratification of reference ranges for VWF:Ag and VWF:RCo with respect to blood group O and non-group O has been recommended [188,189], limited evolving information supports the concept that, despite the ABO blood grouping and associated VWF reference ranges, the major determinant of bleeding symptoms or risk is low VWF [184,190,191]. Therefore, referencing VWF testing results to the population reference range, rather than to ABO-stratified reference ranges, may be more useful clinically.

<table>
<thead>
<tr>
<th>ABO type</th>
<th>Number</th>
<th>VWF:Ag mean (U dL⁻¹)</th>
<th>Range, U dL⁻¹</th>
<th>(IU dL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>456</td>
<td>74.8</td>
<td>35.6–157.0 (41–179)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>340</td>
<td>105.9</td>
<td>48.0–233.9 (55–267)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>196</td>
<td>116.9</td>
<td>56.8–241.0 (65–275)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>109</td>
<td>123.3</td>
<td>63.8–238.2 (73–271)</td>
<td></td>
</tr>
</tbody>
</table>

VWF:Ag, von Willebrand factor antigen.
Modified from Gill et al. [45]. Used with permission. In this publication, VWF:Ag was expressed as U dL⁻¹ (units per deciliter), but the range in IU dL⁻¹ (WHO) is higher for all blood groups, as noted in the values in parentheses (R. R. Montgomery, J. L. Endres and K. D. Friedman, personal communication).

Platelet VWF assays. Platelet VWF studies are performed by some laboratories, including VWF:RCo, VWF:Ag and VWF multimers, using VWF extracted from washed platelets. The methods and interpretations of these studies, however, are not well standardized.

DNA sequencing analysis. DNA sequencing of patient DNA has been used to make a molecular diagnosis of variants of type 2 VWD [192–194], but DNA sequencing is not widely available. Most of the mutations found in types 2B, 2M and 2N VWD cluster in the cDNA that directs the synthesis of specific regions of VWF (Fig. 2) [195]. In the common forms of type 2A VWD, in which the VWF is spontaneously cleaved by ADAMTS13, mutations cluster in the A2 domain (which contains the cleavage site). In the less common type 2A variants of VWD, in which multimer formation is inhibited, the mutations may be scattered throughout the gene. In most persons with type 1 VWD, the genetic mutations have not been established, although several studies are under way to characterize these mutations.

Assays for detecting VWF antibody. Assays for detecting anti-VWF antibodies are not as well established as the assays for detecting antibodies to FVIII in patients with haemophilia A. Some patients with AVWS do appear to have anti-VWF antibodies that decrease the half-life of infused VWF. Although a few antibodies do inhibit VWF function and can be demonstrated in 1:1 mixing studies with normal plasma using the VWF:RCo assay, most anti-VWF antibodies are not inhibitors of VWF function. The presence of these antibodies, however, promotes rapid clearance of VWF. The plasma level of the VWFpp is normally proportionate to the level of VWF:Ag, and the VWFpp level can be measured to aid in the detection of the rapid clearance of VWF. Accelerated plasma clearance of VWF:Ag — as occurs in some patients with AVWS, in those who have certain type 1 VWD variants, or in those who have type 3 VWD and have alloantibodies to VWF — is associated with an increase in the ratio of VWFpp to VWF:Ag [196,197]. Persons with type 3 VWD, with large deletions of the VWF gene, are prone to develop alloantibodies to transfused VWF [198]. Patients who have AVWS, VWF antibodies or mutations that affect VWF clearance can be studied using VWF-survival testing after administration of desmopressin or VWF concentrate.

Making the diagnosis of VWD
Scoring systems and criteria for assessing the bleeding history and the probability of having VWD,
especially type 1 VWD, are evolving and have not yet been subjected to prospective studies outside defined populations [149,189]. Establishing the diagnosis of VWD in persons with type 2 VWD variants and type 3 VWD is usually straightforward, based on the initial VWD tests (VWF:Ag, VWF:RCo and FVIII). Treatment depends on the specific subtype (e.g. type 2A, 2B, 2M or 2N), which is determined by additional tests, including VWF multimer analysis. In contrast, the diagnosis of type 1 VWD is often more difficult [22,46,95,199,200], partly because not all persons who have decreased levels of VWF have a molecular defect in the VWF gene. Whether individuals who do not have an abnormality in the VWF gene should be diagnosed as having VWD or should be given another designation is currently under consideration (see Type 1 VWD vs. Low VWF).

The reasons for reduced VWF levels in many of these persons who have a normal VWF gene sequence are not understood. A ‘low’ VWF level is believed to confer some bleeding risk, despite the presence of a normal VWF gene, and those persons who have clinical bleeding and low VWF concentrations may benefit from treatment to raise the VWF level. Most clinicians would agree that persons having VWF levels <30 IU dL\(^{-1}\) probably have VWD. It is likely that most of these persons have a mutation in the VWF gene. Currently, several large European Union, Canadian and US studies are trying to define that frequency. Persons whose plasma VWF levels are below the lower limit of the laboratory reference range, but higher than 30 IU dL\(^{-1}\), may have VWD but are sometimes referred to as having ‘possible type 1 VWD’ or ‘low VWF’. There is no generally accepted designation for these persons. Although type 3 VWD is usually the result of inheriting two null alleles, the heterozygous carriers in these families do not universally have a history of serious bleeding; therefore, type 3 VWD has been called a recessive disorder [22,46,103].

**Special considerations for laboratory diagnosis of VWD**

**Repeated laboratory testing.** Repeated testing for VWD is sometimes needed to identify low levels of VWF. Stress — including surgery, exercise, anxiety, crying in a frightened child, as well as systemic inflammation, pregnancy or administration of oestrogen or oral contraceptives — can increase plasma levels of VWF and mask lower baseline values. VWF levels vary with the menstrual cycle, and lowest values are detected on days 1–4 of the menstrual cycle. However, the importance of timing of the testing with respect to the menstrual cycle is not clear. Family studies may be helpful to diagnose hereditary decreases in VWF levels.

**Blood sample collection and processing.** Problems may occur in preparing samples for testing. As noted above, anxiety may falsely elevate the VWF and FVIII levels, and the setting for phlebotomy should be as calm as possible. It is important that the sample be obtained by atraumatic collection of blood, drawn into the appropriate amount of citrate anticoagulant. The College of American Pathologists, as well as the Clinical Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards, commonly known as NCCLS), recommends collecting blood into 3.2% citrate, although some laboratories still use 3.8% citrate. Fasting or non-lipaemic samples should be used for testing, and icteric or haemolysed samples may also compromise the quality of testing results [188,201]. If a person has polycythemia or profound anaemia, the amount of anticoagulant should be adjusted on the basis of nomograms designed for this purpose. Blood should be centrifuged promptly to obtain plasma, and the plasma should remain at room temperature if assays are to be completed within 2 h. Whole blood should not be transported on wet ice (or frozen) [202,203]. If plasma samples are frozen, they should be thawed at 37°C to avoid formation of a cryoprecipitate. Plasma assays should be performed on platelet-poor or platelet-free plasma [188]. Although a small number of platelets may not greatly affect studies done on fresh plasma, freezing these samples may result in the release of proteases or platelet membrane particles that affect plasma assays for VWF. Thus, plasmas should be centrifuged carefully. Some laboratories perform double centrifugation to ensure platelet removal. The integrity of samples may suffer during transport to an outside laboratory, and steps should be taken that can best ensure prompt delivery of frozen samples. Table 11 provides additional information about collection and processing of blood and plasma samples for laboratory testing.

**VWF reference standards.** The VWF reference standard is critical to the laboratory diagnosis of VWD. When possible, all laboratory assays of VWF should use the same standard to avoid artifactual discrepancies. Results of VWF assays can be reported in IUs only if they have been referenced to the WHO standard for that analyte. If a reference plasma pool is used, it is usually reported as a percentage of normal, as it cannot be called an IU. To assist the comparison, IUs are usually expressed as IU dL\(^{-1}\) so that the reported values have the same range as values reporting a percentage of normal plasma.
Table 11. Collection and handling of plasma samples for laboratory testing.

Phlebotomy conditions – An atraumatic blood draw limits the exposure of tissue factor from the site and the activation of clotting factors, minimizing falsely high or low values
Patient stress level – Undue stress, such as struggling or crying in children or anxiety in adults, may falsely elevate VWF and FVIII levels. Very recent exercise can also elevate VWF levels.
Additional conditions in the person – The presence of an acute or chronic inflammatory illness may elevate VWF and FVIII levels, as may pregnancy or administration of oestrogen or oral contraceptives
Sample processing – To prevent cryoprecipitation of VWF and other proteins, blood samples for VWF assays should be transported to the laboratory at room temperature. Plasma should be separated from blood cells promptly at room temperature, and the plasma should be centrifuged thoroughly to remove platelets. If plasma samples will be assayed within 2 h, they should be kept at room temperature. Frozen plasma samples should be carefully thawed at 37°C and kept at room temperature for <2 h before assay.
Sample storage – Plasma samples that will be stored or transported to a reference laboratory must be frozen promptly at or below −40°C and remain frozen until assayed. A control sample that is drawn, processed, stored and transported under the same conditions as the tested person’s sample may be helpful in indicating problems in the handling of important test samples.

Laboratory testing variables. Laboratory variables also occur. The variability (CV) of the VWF:RCo assay is high (±20–30%), and the CV of the VWF:Ag assay is also relatively high (±10–20%), as is the CV for the FVIII assay [170,172–174,178,204–206]. The quality of laboratory testing also varies considerably among laboratories (high interlaboratory CV). Coupled with variability of VWF and FVIII contributed by conditions of the patient and the blood sample, the high variability of these three diagnostic tests can contribute to difficulty in diagnosing VWD or classifying the VWD subtype (e.g. type 1 vs. type 2 variant, using the VWF:RCo/VWF:Ag ratio). Some of the more specialized tests, such as VWF multimer analysis likely also have high variability of test performance and interpretation [175,176], and they are often not available at local testing laboratories.

Summary of the laboratory diagnosis of VWD The diagnosis of VWD can be complex, and no single diagnostic approach is suitable for all patients. Improvements in laboratory testing and quality, along with further research into the frequency of mutations of the VWF gene, alterations of other proteins that result in reduced VWF levels, and the correlation of clinical symptoms with laboratory test levels are necessary to place the diagnosis of VWD on a more secure foundation.

Diagnostic recommendations

The recommendations are graded according to criteria described in Table 1. Diagnostic Recommendations I–III summarize the Panel’s patient diagnostic recommendations. Evidence Tables 1–5 are provided in the full online document [10] for recommendations given a grade of B and having two or more references.

The recommendations that follow (Diagnostic Recommendations I, II and III) include specific clinical history, physical findings, laboratory assays, and diagnostic criteria that this Panel suggests will provide the most definitive diagnosis of VWD.

In addition, the Panel suggests the following with regard to laboratory testing (Diagnostic Recommendations II). (i) Tests such as the BT, PFA-100 or other automated functional platelet assays have been used, but there are conflicting data with regard to sensitivity and specificity for VWD [157,159,161]. Therefore, the Panel believes current evidence does not support their routine use as screening tests for VWD. (ii) The Panel believes that platelet-based assays should be used for the ristocetin cofactor method (VWF:RCo assay). (iii) The Panel emphasizes the importance of the timing of the phlebotomy for assays, with the patient at his or her optimal baseline as far as possible. (For example, VWF levels may be elevated above baseline during the second and third trimesters of pregnancy or during oestrogen therapy, during acute inflammation such as the perioperative period, during infections and during acute stress.) The careful handling and processing of the sample are also critical, particularly if the sample will be sent for testing at a remote location.

Laboratory testing should be guided by the history and physical findings (Diagnostic Recommendations I) and the initial laboratory evaluation (Diagnostic Recommendations II). For example, findings of liver disease may lead to a different or additional laboratory evaluation rather than an evaluation for VWD. Diagnostic Recommendations III detail recommendations for synthesis of clinical findings and laboratory test results to make the diagnosis of VWD.

Diagnostic Recommendations I

I. Evaluation of Bleeding Symptoms and Bleeding Risk by History and Physical Examination*

A. Ask the following broad questions:

1. Have you or a blood relative ever needed medical attention for a bleeding problem, or have

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Haemophilia (2008), 14, 171–232

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you been told you had a bleeding problem?

*Grade B, level IIb [135]*

If the answer is ‘Yes’ to either of the broad questions above, ask the additional probes:

1. Have you needed medical attention for bleeding? After surgery? After dental work? With trauma?
2. Have you ever had bruises so large they had lumps?

*Grade B, level IIb [135]*

2. Do you have or have you ever had:

1. Liver or kidney disease?
2. A blood or bone marrow disorder? A high or low platelet count?

If the answer is ‘Yes’ to any of these questions, obtain relevant details.

*Grade C, level IV*

3. Are you currently taking, or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, nonsteroidal anti-inflammatory drugs, clopidogrel)?

If the answer is ‘Yes’, obtain relevant details.

*Grade C, level IV*

B. If answers to questions I.A.1 are positive, ask if the patient or any blood relatives have had the following:

1. A bleeding disorder, such as von Willebrand disease or haemophilia?
2. Prolonged, heavy, or recurrent bleeding from:
   1. Trivial wounds, lasting more than 15 min or recurring spontaneously during the 7 days after the wound?
   2. Surgical procedures, such as tonsillectomy?
3. Bruising with minimal or no apparent trauma, especially if you could feel a lump?
4. Spontaneous nosebleeds that required more than 10 min to stop or needed medical attention?
5. Dental extractions leading to heavy, prolonged, or recurrent bleeding?
6. Blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach or a polyp in the colon), that required medical attention?
7. Anaemia requiring treatment or received a blood transfusion?
8. For women, heavy menses, characterized by the presence of clots larger than 1 inch and/or changing a pad or tampon more than hourly or resulting in anaemia or low iron level?

If answers to questions I.B.1–8 are positive, obtain relevant specific information, including history of treatment (e.g. blood transfusion).

*Grade B, level IIb [135,148]*

See Evidence Table 1 [10] for additional detail and information.

C. Perform a physical examination to include evaluation for

1. Evidence for bleeding disorder, including size, location, and distribution of ecchymoses (e.g. truncal), haematomas, petechiae, and other evidence of recent bleeding and/or anaemia.

*Grade C, level IV*

2. Evidence that suggests other causes or risks of increased bleeding, such as jaundice or spider angiomas (liver disease), splenomegaly, arthropathy, joint and skin laxity (e.g. Ehlers-Danlos syndrome), telangiectasia (e.g. hereditary haemorrhagic telangiectasia), or evidence of anatomic lesion on gynaecologic examination.

*Grade C, level IV*

*Summarized in Fig. 3 and Table 9.*

**Diagnosis**

**Diagnosis Recommendations II**

**II. Evaluation by Laboratory Testing***

A. Initial laboratory evaluation for the aetiology of a bleeding disorder should include the following:

1. A complete blood cell count (including platelet count), prothrombin time, activated partial thromboplastin time (PTT), and optionally either thrombin time or fibrinogen level.
2. If laboratory abnormalities besides the PTT are present (the platelet count may also be decreased in type 2B von Willebrand disease [VWD]), in conjunction with the history and physical examination findings, consider bleeding disorders other than VWD or additional underlying diseases.
3. If the mucocutaneous bleeding history is strong, consider performing initial VWD assays at the first visit (see II.B, below).
4. If there are no abnormalities on initial blood testing or if there is an isolated prolonged PTT that corrects in the 1:1 mixing study, the following 3 tests for VWD should be performed (II.B, below), unless another cause for bleeding has been identified and VWD is not likely (see Fig. 4). For further laboratory evaluation, physicians may consider referral to a haemostasis center because of the special sample handling and testing requirements (see Table 11).

*Grade C, level IV*

B. Initial tests for diagnosing or excluding VWD include the following three tests:
2. Von Willebrand factor antigen (VWF:Ag).
3. Factor VIII activity (FVIII).

**Grade B, level III** [3,45,170,171]

See Evidence Table 2 [10] for additional detail and information.

C. If any of the above test results is abnormally low, a discussion with or a referral to a haemostasis expert is appropriate. In addition to repeating the initial three tests (in most cases), the specialist may recommend appropriate studies from the following:

1. The first set of additional tests may include
   a. Evaluation of the ratio of VWF activity (VWF:RCo and/or von Willebrand factor collagen-binding activity [VWF:CB]) to VWF:Ag (only in laboratories that have defined reference ranges for the ratio[s]).
   **Grade B, level III** [72,73,93,158,170,185]
   See Evidence Table 3 [10] for additional information and detail.
   b. VWF multimer study.
   **Grade B, level III** [176]
   c. Ristocetin-induced platelet aggregation (RIPA).
   **Grade B, level III** [48]
   d. VWF:CB.
   **Grade B, level IIb** [170,180,181]
   See Evidence Table 4 [10] for additional information and detail.

2. Studies in selected patients, especially those who have discordantly low FVIII activity compared to von Willebrand factor (VWF) levels and who are suspected of having type 2N VWD, should include a FVIII binding assay (VWF:FVIIIB).
   **Grade B, level IIb** [79,80,183]

III. Making the Diagnosis

A. **Clinical criteria.** These criteria include personal and/or family history and/or physical evidence of mucocutaneous bleeding. Until further validation of scoring systems and criteria for assessing bleeding history and the probability of von Willebrand disease (VWD), especially type 1 VWD, the Expert Panel suggests that an increasing number of positive responses to the questions about bleeding (Diagnostic Recommendations I; Fig. 3; Table 9) and abnormal findings on physical examination increase the likelihood that an individual has a bleeding disorder, including possible VWD.

AND

B. **Laboratory criteria.** The values in the following table represent prototypical cases without additional

<table>
<thead>
<tr>
<th>Condition</th>
<th>VWF:RCo (IU dL⁻¹)</th>
<th>VWF:Ag (IU dL⁻¹)</th>
<th>FVIII</th>
<th>Ratio of VWF:RCo/VWF:Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>&lt;30*</td>
<td>&lt;30*</td>
<td>↓ or normal</td>
<td>&gt;0.5 to 0.7</td>
</tr>
<tr>
<td>Type 2A</td>
<td>&lt;30*</td>
<td>&lt;30–200&gt;†</td>
<td>↓ or normal</td>
<td>&lt;0.5 to 0.7</td>
</tr>
<tr>
<td>Type 2B</td>
<td>&lt;30*</td>
<td>&lt;30–200&gt;†</td>
<td>↓ or normal</td>
<td>&lt;0.5 to 0.7</td>
</tr>
<tr>
<td>Type 2M</td>
<td>&lt;30*</td>
<td>&lt;30–200&gt;†</td>
<td>↓ or normal</td>
<td>&lt;0.5 to 0.7</td>
</tr>
<tr>
<td>Type 2N</td>
<td>30–200</td>
<td>30–200</td>
<td>↓</td>
<td>&gt;0.5 to 0.7</td>
</tr>
<tr>
<td>Type 3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>↓↓↓ (&lt;10 IU dL⁻¹)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>‘Low VWF’</td>
<td>30–50</td>
<td>30–50</td>
<td>Normal</td>
<td>&gt;0.5 to 0.7</td>
</tr>
<tr>
<td>Normal</td>
<td>50–200</td>
<td>50–200</td>
<td>Normal</td>
<td>&gt;0.5 to 0.7</td>
</tr>
</tbody>
</table>

FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

↓ refers to a decrease in the test result compared to the laboratory reference range.

*Less than 30 IU dL⁻¹ is designated as the level for a definitive diagnosis of VWD; some patients with type 1 or type 2 VWD have levels of VWF:RCo and/or VWF:Ag of 30–50 IU dL⁻¹.

*The VWF:Ag in the majority of individuals with type 2A, 2B or 2M VWD is <50 IU dL⁻¹.

See Evidence Table 5 [10] for additional information and detail.

3. Additional studies in selected persons may include the following:
   a. Gene sequencing.
   **Grade C, level IV**
   b. Assays for antibodies to VWF.
   **Grade C, level IV**
   c. Platelet-binding studies.
   **Grade B, level III** [177]

*Laboratory testing should be guided by the history and physical findings (Diagnostic Recommendations I) and results of the initial laboratory evaluation (II.A, above). For example, findings of liver disease may lead to a different or additional laboratory evaluation rather than an evaluation for VWD (II.B, above).
von Willebrand factor (VWF) (or other disease) abnormalities in the patient. In practice, exceptions occur, and repeated testing and clinical experience are important and may be necessary for interpretation of laboratory results.

1. Although published evidence is limited, for defining the ratio of VWF:RCo/VWF:Ag to use for distinguishing type 1 VWD versus type 2 VWD variants (A, B, or M), the Expert Panel recommends a ratio of less than 0.5–0.7 until more laboratories clearly define a reference range using large numbers of normal subjects and persons with type 1 VWD and type 2 VWD variants. 

Grade C, level IV [72,73,93,158,184,185]

2. The Panel currently recommends that 30 IU dL\(^{-1}\) be used as the cutoff level for supporting the definite diagnosis of VWD for the following reasons:

- There is a high frequency of blood type O in the United States, and it is associated with ‘low’ VWF levels [45].
- Bleeding symptoms are reported by a significant proportion of normal individuals [134–136,148].
- No abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels.

Grade C, level IV [102–104]

Non-replacement therapy with desmopressin to elevate VWF

Mechanism of action of desmopressin 

Desmopressin (DDAVP) is a synthetic derivative of the antidiuretic hormone, vasopressin. Desmopressin has been used to treat VWD for more than 25 years, and its pharmacology, mechanism of action and indications have been reviewed extensively [210–212]. Desmopressin stimulates the release of VWF from endothelial cells through its agonist effect on vasopressin V2 receptors [210,211,213]. The mechanism by which desmopressin increases plasma concentration of VWF is probably through cyclic adenosine monophosphate (cAMP)-mediated release of VWF from endothelial cell Weibel-Palade bodies [213,214]. FVIII levels also increase acutely after administration of desmopressin, although the FVIII storage compartment and the mechanism of release by desmopressin have not been fully elucidated [12,215]. Desmopressin induces the release of tissue plasminogen activator (tPA) [216,217]. However, the secreted tPA is rapidly inactivated by plasminogen activator inhibitor type 1 (PAI-1) and does not appear to promote fibrinolysis or bleeding after desmopressin treatment.

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Table 12. Intravenous desmopressin effect on plasma concentrations of FVIII and VWF in normal persons and persons with VWD.

<table>
<thead>
<tr>
<th>Group/source</th>
<th>Number</th>
<th>Mean increase (fold)*</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [218]</td>
<td>10</td>
<td>NA</td>
<td>3.3</td>
</tr>
<tr>
<td>Lethagen et al. [219]</td>
<td>10</td>
<td>NA</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>VWD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [218]</td>
<td>15</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>de la Fuente et al. [220]</td>
<td>13</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Mannucci et al. [94]</td>
<td>7</td>
<td>9.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Rodeghiero et al. [221]</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mannucci et al. [222]</td>
<td>15</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Revel-Vilk et al. [223]</td>
<td>56</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Federici et al. [224]</td>
<td>26</td>
<td>3.1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 1, Vicenza (ultralarge multimers)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [94]</td>
<td>6</td>
<td>9.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Rodeghiero et al. [221]</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 1, severe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revel-Vilk et al. [223]</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Federici et al. [224]</td>
<td>26</td>
<td>3.1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 1, severe with normal platelet VWF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodeghiero et al. [225]</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mannucci et al. [101]</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 1, platelet low</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [101]</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rodeghiero et al. [221]</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 2A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de la Fuente et al. [220]</td>
<td>7</td>
<td>6.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Revel-Vilk et al. [223]</td>
<td>5</td>
<td>4.2</td>
<td>NA</td>
</tr>
<tr>
<td>Rever-Vilk et al. [223]</td>
<td>15</td>
<td>2.6</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 2B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casonato et al. [66]</td>
<td>4</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>McKeown et al. [226]</td>
<td>3</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Castaman and Rodeghiero [227]</td>
<td>33</td>
<td>Normalized in 18/33</td>
<td>Normalized in 33/33</td>
</tr>
<tr>
<td><strong>Type 2M</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federici et al. [224]</td>
<td>21</td>
<td>3.3</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 2N</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazurier et al. [228]</td>
<td>8</td>
<td>1.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Federici et al. [224]</td>
<td>4</td>
<td>3.8</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Type 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castaman et al. [229]</td>
<td>6</td>
<td>1.8</td>
<td>8.6</td>
</tr>
</tbody>
</table>

FVIII, factor VIII; NA, not available; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor.

*Response defined as twofold increase AND to at least 30 IU dL−1 VWF:RCo and FVIII.

†Response defined as twofold increase AND to at least 30 IU dL−1 VWF:RCo and FVIII.

Table 12 displays published reports of desmopressin effects on laboratory assays of VWF and FVIII in normal persons and persons who have various subtypes of VWD [66,94,101,218–229]. When administered intravenously (i.v.) to normal persons as well as to patients with VWD or mild haemophilia, desmopressin consistently increases plasma VWF and FVIII...
from twofold to more than fivefold over baseline levels [94,215,218–223]. Children younger than 2 years have a lower response rate than older children [223]. Two controlled prospective studies in healthy volunteers form the basis for desmopressin dosing recommendations [218,219]. Maximal FVIII response was determined at 0.3 µg kg\(^{-1}\) in both studies, while maximal VWF release data were determined at 0.2 and 0.3 µg kg\(^{-1}\) in the same two studies. On the basis of these data, standard dosing of desmopressin is 0.3 µg kg\(^{-1}\) given i.v. in 30–50 mL of normal saline over 30 min, with peak increments of FVIII and VWF 30–90 min after the infusion [215,219,220,230]. Nasal administration of high-dose desmopressin acetate (Stimate; CSL Behring, King of Prussia, PA, USA) is often effective for minor bleeding, but i.v. administration is the preferred route for prophylaxis of surgical bleeding and for treatment of major haemorrhage.

A retrospective review of desmopressin administration to 56 children who had non-severe type 1 VWD found a 91% response rate, defined as a twofold increase in FVIII and VWF activity, to at least 30 IU dL\(^{-1}\) [223]. In a small case series of VWD patients, the consistency of FVIII increments and the responses of the BT after a second test dose of desmopressin were within 10–20% of the initial values [221]. Evidence shows that response to desmopressin diminishes with repeated doses, probably because of depletion of the VWF storage compartment [215,218]. However, when desmopressin was given in four daily doses to 15 patients who had type 1 VWD, an increase in FVIII activity of at least twofold was found in 100% of the patients after the first administration, in 80% after the second, in 87% after the third and in 74% after the fourth administration [222].

Consistency of response to desmopressin has been studied using three to four once-daily doses [218,222]. A series of 15 type 1 VWD patients showed a mean increase of VWF:RCo to fivefold above baseline after the first dose of desmopressin, significantly decreased response to fourfold after the second daily dose, and no significant change in response between the second and third and third and fourth doses [222]. The proportion of VWD patients attaining at least a twofold increase in FVIII activity after the second to fourth daily doses – 80% after the second daily dose of desmopressin to 74% after the fourth dose – was substantially higher than that for haemophilia A patients (55% vs. 37%). There is no published evidence regarding response to desmopressin given every 12 h to compare with daily dosing of desmopressin. In addition to tachyphylaxis, hyponatraemia may complicate repeated desmopressin dosing, and fluid restriction and serum sodium monitoring are recommended.

Desmopressin can also be administered subcutaneously (s.c.) or intranasally [218,219,230]. The effective s.c. dose is identical to the i.v. dose, but the s.c. preparation is not available in the United States. The preparation of desmopressin for nasal instillation (Stimate) contains 150 µg of desmopressin per metered nasal puff (0.1 mL of a 1.5 mg mL\(^{-1}\) solution). The dose is one puff for persons who weigh <50 kg and two puffs (one puff to each nostril) for persons weighing 50 kg or more. Although the intrasubject and intersubject CV for reproducibility of nasal spray effect is good, nasal absorption is variable and all patients with VWD and who are responsive to i.v. desmopressin should undergo a trial of nasal desmopressin (Stimate) to measure FVIII and VWF response before using it [219]. When used for epistaxis, intranasal desmopressin ideally is delivered into the non-bleeding nostril. Persons who have inadequate plasma responses to i.v. desmopressin will not respond to intranasal desmopressin.

Another nasal formulation of desmopressin for enuresis contains 10 µg per puff (about 7% of the Stimate concentration); however, this preparation is not suitable for treatment of VWD. Patients and parents must be carefully instructed regarding the two concentrations of nasal desmopressin — the one used for bleeding (1.5 mg mL\(^{-1}\)) and the one used for antidiuretic hormone replacement (diabetes insipidus) and bedwetting (0.1 mg mL\(^{-1}\)) — to avoid accidental underdosing for VWD.

**Monitoring of VWD patients receiving desmopressin** Treatment of patients who have VWD with desmopressin should be based on results of a therapeutic trial, ideally one performed in patients in a non-bleeding state and before general clinical use. Although the pattern of desmopressin responsiveness is fairly consistent within VWF subtypes, population results should not be used to plan treatment of individual patients (Table 12). VWF:RCo and FVIII activities should be measured in all VWD patients at baseline and within 1 h after administering desmopressin. Additional assay of VWF:RCo and FVIII, done 2–4 h after desmopressin administration, will evaluate for shortened survival and should be considered for patients who have a history of poor response to treatment [43].

According to conservative definitions of laboratory response, the majority of patients with type 1 VWD respond adequately to desmopressin (Table 12).
Single infusions of desmopressin for common bleeding episodes — such as epistaxis, simple dental extraction or menorrhagia — do not usually require laboratory monitoring. Patients should be monitored for VWF:RCo activity as well as FVIII activity around major surgical procedures or major bleeding events. For major surgical procedures or bleeding events, patients with VWD should be referred to hospitals with in-house or daily laboratory availability of FVIII and VWF:RCo activity assays. Care should be taken to monitor serum electrolytes, especially after surgery or multiple doses of desmopressin. Adult patients, especially those who are elderly, should be evaluated for cardiovascular disease before using desmopressin because myocardial infarction rarely has been precipitated by desmopressin therapy in patients with haemophilia or uraemia [231–233].

Pharmacokinetics of VWF and FVIII after desmopressin After stimulation with desmopressin, released VWF and FVIII circulate with an apparent half-life characteristic of the patient’s own proteins, or approximately 8–10 h for both proteins in normal individuals [215]. Type 2 VWF proteins that are released by desmopressin increase in concentration but retain their intrinsic molecular dysfunction [234]. For this reason, desmopressin has been efficacious in only a minority of patients with types 2A or 2M VWD. Therefore, monitoring is necessary to document adequate correction of VWF:RCo. Type 2N VWF lacks FVIII stabilization; consequently, patients with 2N VWF release FVIII and the abnormal VWF protein as expected, but the survival of released FVIII may be severely decreased, with an apparent plasma half-life as low as 2 h, depending on the mutation [163,228]. Emerging information suggests that some individuals with type 1 VWD have accelerated plasma clearance of VWF and may benefit from trial testing of VWF:RCo 2–4 h after a dose of desmopressin [42,235].

After infusion of desmopressin into patients with type 2B VWD, VWF multimers of larger but still somewhat less than normal molecular weight can be detected in plasma after 15–30 min, with persistence throughout 4 h of study [65,163,234,236]. Although formal pharmacokinetic studies have not been reported for type 2B VWD, VWF:RCo activity increases were less than that seen in type 1 VWD with an apparent half-life of approximately 4 h [65,226]. Bleeding time response to desmopressin in type 2B VWD is inconsistent [226,227].

Clinical response to desmopressin in VWD The clinical effectiveness of desmopressin to prevent or control bleeding depends, in large part, on the plasma VWF:RCo or FVIII activity achieved after drug administration, which in turn depends primarily on the basal levels of plasma FVIII and VWF:RCo and to a lesser extent on the underlying qualitative VWF defect [66,94,101,218–229]. Table 13 and Evidence Tables 7–11 [10] summarize published data on the clinical response when using desmopressin in conjunction with common surgical procedures [133,215,220,223,225,227,229,237–247]. All data were derived from retrospective studies and small case series; there are no randomized-clinical trials of the use of desmopressin in persons with VWD.

Table 13. Clinical results of desmopressin treatment in patients with von Willebrand disease*.

<table>
<thead>
<tr>
<th>Surgical prophylaxis</th>
<th>Number</th>
<th>Frequency</th>
<th>Duration</th>
<th>Other treatment</th>
<th>Bleeding outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental procedures</td>
<td>113</td>
<td>Once</td>
<td>Once or twice</td>
<td>Antifibrinolitics</td>
<td>Excellent/good in 109/113</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>9</td>
<td>Daily</td>
<td>1–7 days</td>
<td>Antifibrinolitics 2/7</td>
<td>Delayed bleeding in 2/9 requiring extended desmopressin treatment for 3 and 6 days</td>
</tr>
<tr>
<td>[215,220,238,239]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery [215,220,229,239,242,255,380]</td>
<td>26</td>
<td>Daily</td>
<td>1–5 days</td>
<td></td>
<td>Excellent/good in 25/26 Haemorrhage after 1 rhinoplasty</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primarily tonsillectomy and adenoidectomy [241–247]</td>
<td>146</td>
<td>Once or twice daily</td>
<td>1–7 days</td>
<td>Antifibrinolitics in most for 7 days</td>
<td>Excellent/good in 125/146</td>
</tr>
<tr>
<td>Primarily tonsillectomy/adenoidectomy [261]</td>
<td>119</td>
<td>NA</td>
<td>2 days</td>
<td></td>
<td>Excellent/good in 105/119</td>
</tr>
<tr>
<td>Otorologic surgery [242]</td>
<td>6</td>
<td>Daily</td>
<td></td>
<td></td>
<td>Excellent/good in 6/6</td>
</tr>
</tbody>
</table>

NA, not available.

*For additional detail and information, see Evidence Tables 7–11 [10].
Whether desmopressin will be adequate for prophylaxis around surgery or for treatment of bleeding events in persons with type 1 VWD depends on the severity of the haemostatic challenge and the time required for healing. Major surgery requires haemostasis for 7–14 days [239,248–253], whereas minor surgical procedures can be treated adequately in 1–5 days [239,245,246,253]. If treatment is necessary for more than 3 days, VWF concentrate is usually given to supplement therapy with desmopressin [239,246]. Currently, however, expert opinions are divided regarding the risk of delayed haemorrhage 5–10 days after a bleeding challenge in VWD patients, e.g., those who have had tonsillectomy or given birth. In small case series, persons with type 1 VWD Vicenza manifested an exaggerated response to desmopressin [43,94,221]. Individuals with type 2N VWD exhibit a brisk rise in plasma FVIII after receiving desmopressin, but they have a mean FVIII half-life of only 3 h because of deficient FVIII stabilization by the defective VWF [228]. Persons with low-platelet VWF or type 2A VWD have a low likelihood of having a clinically relevant desmopressin response, but they may warrant a desmopressin trial [221,224]. Type 2B VWD previously was a contraindication to desmopressin therapy because platelet counts usually fell after desmopressin stimulation [254]. However, thrombocytopenia after desmopressin in type 2B VWD is usually transient and often is not associated with bleeding or thrombosis [255]. In patients with type 2B VWD, decrease in platelet count after desmopressin administration has been considered ‘pseudothrombocytopenia’ by some authors because it is related to platelet agglutination in vitro rather than in vivo agglutination and clearance [65,236]. Therefore, desmopressin may be cautiously considered for patients with type 2B VWD. Patients with type 3 VWD almost never experience a clinically relevant rise in VWF:RCo or FVIII activities, and desmopressin is not considered clinically useful in these patients [223,224].

Complications and toxic effects of desmopressin Minor adverse effects of desmopressin are common and include facial flushing, transient hypertension or hypotension, headache or gastrointestinal upset [211,212,256], but these effects rarely limit clinical use. Water retention after a dose of desmopressin, with an increase in urinary osmolality, is universal; however, decreased serum sodium in otherwise healthy adults is variable and is related to multiple doses [256,257]. In the case of repeated dosing, all patients should be instructed to limit fluid intake to maintenance levels for 24 h [258–260]. Prophylactic use of desmopressin complicates the management of fluids and electrolytes for surgery or during childbirth. Seizures have been associated with hyponatraemia after desmopressin administration, primarily in young children [257,260]. Most paediatric haematologists do not use desmopressin in children <2 years old [223,260,261].

Myocardial infarction after treatment with desmopressin has been reported, although rarely, in patients with mild haemophilia A [231,233,262]. Desmopressin should be avoided in patients who are at very high risk for cardiovascular or cerebrovascular disease, especially the elderly, as underlying inhibition of plasminogen activation with desmopressin-related vasoconstriction contributes additional prothrombotic effects in these patients [263]. Because of reported complications in other patient populations, desmopressin should be used with caution for brain, ocular and coronary artery surgeries [232,264,265], and VWF concentrate replacement generally is used in these settings. Desmopressin does not appear to increase myometrial contractility greatly; consequently, pregnancy is not an absolute contraindication [266–269] but use of desmopressin is rarely indicated (see Pregnancy).

Replacement therapies to elevate VWF concentration: VWF concentrates

As of January 2007, Humate-P (CSL Behring) and Alphanate SD/HT (Grifols USA, Los Angeles, CA, USA) are plasma-derived concentrates licensed in the United States to replace VWF in persons who have VWD. One other plasma derivative — Koate DVI (Talecris Biotherapeutics USA, Research Triangle Park, NC, USA) — is licensed in the United States to treat haemophilia and has been used off-label for VWD. These products are not identical, having differing ratios of FVIII to VWF, and should not be considered as interchangeable [270–272]. All these products are manufactured at US-licensed facilities from pooled plasma collected from paid donors.

Products that contain FVIII and little or no VWF are generally not useful to treat VWD, but in rare circumstances these products may be used to treat patients who have antibody-mediated AVWS [273]. These products include the plasma-derived concentrates Monoclate P (CSL Behring), MonarCTM (Blood Diagnostics, Inc., Irmo, SC, USA) and HemoPlast M (Baxter Healthcare Corp., Deerfield, IL, USA) and recombinant products Helixate FS (CSL Behring), Kogenate FS (Bayer HealthCare, Berkeley, CA, USA), Recombinate (Baxter Healthcare), Advate

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Humate-P, a lyophilized concentrate of purified VWF and FVIII, contains other plasma proteins, including fibrinogen and albumin. In Humate-P, the quantity of the large, most haemostatically active multimers of VWF is decreased compared to fresh plasma [274]. When reconstituted at the recommended volume, each millilitre of the product contains 50–100 IU mL\(^{-1}\) VWF:RCo and 20–40 IU mL\(^{-1}\) FVIII activity [275]. The median half-life of VWF:RCo activity was 10.3 h (range: 6.4–13.3) in one study [275] and 11.3 h in another study [248]. The product is indicated for use in adult and paediatric patients for treatment of spontaneous and trauma-induced bleeding when use of DDAVP is thought or known to be inadequate or contraindicated. Humate-P has received FDA approval for use in prophylactic management of surgery and invasive procedures in patients with VWD.

Alphanate SD/HT is a lyophilized concentrate of VWF and FVIII and other plasma proteins. It is prepared from pooled human plasma by cryoprecipitation of FVIII, fractional solubilization and further purification using heparin-coupled, cross-linked agarose. Upon reconstitution to the recommended volume, each millilitre of product contains 40–180 IU mL\(^{-1}\) FVIII activity and not less than 16 IU mL\(^{-1}\) VWF:RCo activity [276]. The median half-life for VWF:RCo activity was 6.91 h (mean, 7.46 ± 3.20 h; range: 3.68–16.22) [276]. The product is indicated for bleeding prophylaxis in patients with VWD, except type 3, who are undergoing surgical or invasive procedures and in whom desmopressin (DDAVP) is either ineffective or contraindicated.

Adverse reactions to VWF concentrates are rare but include allergic and anaphylactic symptoms, urticaria, chest tightness, rash, pruritus and oedema [250]. If these reactions occur, the infusion should be stopped, and appropriate treatment should be given as required. These products should be used with caution in patients who have known risk factors for thrombosis, as there have been a few reports of venous thromboembolism associated with high levels of FVIII [277,278]. Risk factors include old age, previous thrombosis, obesity, surgery, immobility, oestrogen therapy and use of antifibrinolytic therapy. If patients receive VWF replacement therapy continuously for several days, it has been recommended that FVIII levels be monitored to avoid unacceptably high levels [212,278].

Each of the products that contains VWF:RCo activity differs significantly in their ratios of VWF:RCo to FVIII [249,279], and the dose or frequency of dosing should not be assumed to be the same for all. The ratio of VWF:RCo to FVIII for Humate-P in various reports is 2.7, 2 and 1.6; for Koate-DVI, the ratio is 1.2 and 0.8 and for Alphanate, the ratio is 0.5. These products also differ in their relative levels of high-molecular-weight multimers. Koate-DVI, in particular, has fewer large VWF multimers compared to Alphanate SD/HT, which has fewer than Humate-P or normal plasma [272,281,282]. Recombinant VWF has been prepared and evaluated in animal models [283] but is not available for use in humans.

Cryoprecipitate, derived from plasma, historically has been used to treat haemophilia A and VWD. Although cryoprecipitate is not required to have a specified level of VWF, the final product must have on average at least 80 units of FVIII per standard donor unit [284]. Currently, cryoprecipitate is used under rare circumstances to treat VWD, such as when potential exposure to infectious agents can be limited by using directed donations to prepare the product [285]. However, the use of cryoprecipitate is strongly discouraged by the National Hemophilia Foundation, except in life- or limb-threatening situations when no VWF concentrate is available, because cryoprecipitate is not virally inactivated [286]. In developing countries, patients with VWD may have no other options, because virally inactivated plasma concentrates are not available or are too expensive [280], but use of cryoprecipitate poses a serious risk of disease transmission [287].

VWF concentrates are dosed primarily on the basis of labelled VWF:RCo units and secondarily on the basis of labelled FVIII units. A dosing trial with pharmacokinetic laboratory monitoring should be considered before major surgery for selected patients with type 3 VWD or AVWS who are at risk for poor VWF recovery because of inhibitors. Use of VWF concentrates to prevent or control bleeding has been clinically efficacious, as shown in Table 14. The ultimate goal of surgical prophylaxis is to achieve a therapeutic level of 100 IU dL\(^{-1}\) of VWF:RCo and, at least for the first 3 days of treatment, a nadir of 50 IU dL\(^{-1}\) of VWF:RCo, as well as similar targets for FVIII [248,250–253,288]. Successful surgical haemostasis was reported with the use of continuous infusion after initial bolus infusion at rates of 1–2 U kg\(^{-1}\) per hour of VWF:RCo [249].

Replacement therapy, using a VWF concentrate, is indicated for severe bleeding events or major surgery in patients with types 2 and 3 VWD as well as in patients with type 1 VWD and who are unresponsive to desmopressin or require protracted therapy, or
Table 14. Efficacy of VWF replacement concentrate for surgery and major bleeding events*.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number</th>
<th>Uses</th>
<th>Loading dose (VWF:RCo IU dL(^{-1}))</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michiels et al. [252]</td>
<td>5</td>
<td>Surgery</td>
<td>60–80</td>
<td>100% Excellent–good</td>
</tr>
<tr>
<td>Thompson et al. [253]</td>
<td>42</td>
<td>Surgery</td>
<td>82.3</td>
<td>100% Excellent–good</td>
</tr>
<tr>
<td>Gill et al. [403]</td>
<td>53</td>
<td>Bleeding events</td>
<td>67</td>
<td>98% Excellent–good</td>
</tr>
<tr>
<td>Lillcrap et al. [250]</td>
<td>344/73</td>
<td>Bleeding events/surgery</td>
<td>55.3/69.1</td>
<td>99% Excellent–good</td>
</tr>
<tr>
<td>Nina-Whalley et al. [239]</td>
<td>10</td>
<td>Surgery</td>
<td>54</td>
<td>100% Excellent–good</td>
</tr>
<tr>
<td>Lubetsky et al. [251]</td>
<td>3/9</td>
<td>Bleeding events/surgery</td>
<td>39.5</td>
<td>92.5% Excellent–good</td>
</tr>
<tr>
<td>Dobrkovska et al. [248]</td>
<td>73</td>
<td>Surgery</td>
<td>80(^1)</td>
<td>99% Excellent–good</td>
</tr>
<tr>
<td>Hanna et al. [249]</td>
<td>5</td>
<td>Surgery</td>
<td>25–100(^15)</td>
<td>100% Excellent–good</td>
</tr>
<tr>
<td>Kreuz et al. [246]</td>
<td>26/41</td>
<td>Bleeding events/surgery</td>
<td>10–50(^5)</td>
<td>100% Excellent–good</td>
</tr>
<tr>
<td>Scharrer et al. [288]</td>
<td>66/70</td>
<td>Bleeding events/surgery</td>
<td>20–80(^5)</td>
<td>100% Excellent–good</td>
</tr>
</tbody>
</table>

FVIII, factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
*For additional details and information, see Evidence Table 12 [10].
\(^1\)Loading dose (VWF:RCo IU dL\(^{-1}\)) reported as median except for Lubetsky et al. [251] (mean).
\(^5\)Continuous infusion was used after the loading dose.
\(^1\)Loading dose (FVIII IU dL\(^{-1}\)).

Table 15. Suggested durations of VWF replacement for different types of surgical procedures.

<table>
<thead>
<tr>
<th>Major surgery, 7–14 days*</th>
<th>Cardiothoracic</th>
<th>Caesarean delivery</th>
<th>Craniotomy</th>
<th>Hysterectomy</th>
<th>Open cholecystectomy</th>
<th>Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor surgery, 1–5 days*</td>
<td>Biopsy: breast, cervical</td>
<td>Complicated dental extractions</td>
<td>Gingival surgery</td>
<td>Central line placement</td>
<td>Laparoscopic procedures</td>
<td></td>
</tr>
<tr>
<td>Other procedures, if uncomplicated, single VWF treatment</td>
<td>Cardiac catheterization</td>
<td>Cataract surgery</td>
<td>Endoscopy (without biopsy)</td>
<td>Liver biopsy</td>
<td>Lacerations</td>
<td></td>
</tr>
<tr>
<td>Simple dental extractions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VWD, von Willebrand disease; VWF, von Willebrand factor.
*Individual cases may need a longer or shorter duration depending on the severity of VWD and the type of procedure.

Table 16. Initial dosing recommendations for VWF concentrate replacement for prevention or management of bleeding.

<table>
<thead>
<tr>
<th>Major surgery/bleeding</th>
<th>Loading dose*</th>
<th>Maintenance dose</th>
<th>Monitoring</th>
<th>Therapeutic goal</th>
<th>Safety parameter</th>
<th>May alternate with desmopressin for latter part of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40–60 U kg(^{-1})</td>
<td>20–40 U kg(^{-1}) every 8–24 h</td>
<td>VWF:RCo and FVIII trough and peak, at least daily</td>
<td>Trough VWF:RCo and FVIII &gt;50 IU dL(^{-1}) for 7–14 days</td>
<td>Do not exceed VWF:RCo 200 IU dL(^{-1}) or FVIII 250–300 IU dL(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Minor surgery/bleeding</td>
<td>30–60 U kg(^{-1})</td>
<td>20–40 U kg(^{-1}) every 12–48 h</td>
<td>VWF:RCo and FVIII trough and peak, at least once</td>
<td>Trough VWF:RCo and FVIII &gt;50 IU dL(^{-1}) for 3–5 days</td>
<td>Do not exceed VWF:RCo 200 IU dL(^{-1}) or FVIII 250–300 IU dL(^{-1})</td>
<td></td>
</tr>
</tbody>
</table>

FVIII, factor VIII; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor activity.
*Loading dose is in VWF:RCo IU dL\(^{-1}\).
of known risk factors for thrombosis [277–279]. In all patients who have VWD and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended levels of VWF:RCo and FVIII, perform proper thrombotic-risk assessment, and institute appropriate preventive strategies.

Human platelets contain 10–15% of total blood VWF, and platelet transfusions have been used successfully to treat bleeding in VWD patients [289,290]. Platelet transfusion therapy should be considered as an adjunctive source of VWF, especially in patients with type 3 or platelet-low VWD and PLT-VWD, to control bleeding that is non-responsive or poorly responsive to replacement therapy with VWF concentrate.

Other therapies for VWD

Antifibrinolytics The antifibrinolytic drugs aminocaproic acid and tranexamic acid are agents that inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilize clots that have formed. Studies in haemophilia and in prostatectomy provide the basis for initial trials of antifibrinolytic agents in VWD [291]. The drugs can be used orally or i.v. to treat mild mucocutaneous bleeding in patients with VWD. In patients with mild-to-moderate VWD, tranexamic acid given topically in the oral cavity (’swish and swallow or spit’) every 6 h has been used for prophylaxis in dental surgery, in combination with applied pressure, other topical agents and suturing of surgical sites [237]. The evidence for the effectiveness of local application of these agents is based on clinical case series [292], but this route of administration is not currently FDA approved. When desmopressin or VWF/FVIII concentrates are indicated, the use of antifibrinolytic agents as adjuncts to desmopressin or VWF concentrates has been helpful in controlling bleeding, such as in the oral cavity [133,220,225,229,237–240] and in the gastrointestinal and genitourinary tracts.

The usual adult dose of aminocaproic acid is 4–5 g as a loading dose orally or i.v. (1 h before invasive procedures), and then 1 g h⁻¹, i.v. or orally, or 4–6 g every 4–6 h orally, until bleeding is controlled, or for 5–7 days postoperatively [212]. Total daily dose of aminocaproic acid is limited to 24 g per 24 h to minimize potential adverse effects. Weight-based dosing is required in children and can also be used in adults (50–60 mg kg⁻¹) [212,292]. Lower doses (25 mg kg⁻¹) may be effective and can be used when gastrointestinal tract adverse effects interfere with therapy. Tranexamic acid is given i.v. at a dose of 10 mg kg⁻¹ every 8 h [212]. The oral form is not currently available in the United States, and use of the i.v. form as an oral rinse (’swish and swallow’ approach) is not an FDA-approved indication. The package insert for each drug should be consulted for more detailed guidance and for a full list of risks and contraindications. Both drugs can cause nausea and vomiting; less frequent but serious adverse effects include thrombotic complications. Both drugs are excreted renally, and dose adjustment or avoidance is advisable when significant renal insufficiency is present. Disseminated intravascular coagulation and bleeding from the renal parenchyma or upper urinary tract are relative contraindications to antifibrinolytic agents. Renovascular thrombi have followed use of antifibrinolytic agents in patients with disseminated intravascular coagulation and have caused renal failure. Patients have also experienced urinat tract obstruction with upper urinary tract bleeding, related to large clots in the renal pelvis or lower urinary tract. Changes in colour vision during therapy with tranexamic acid require cessation of the drug and ophthalmologic examination.

Topical agents Topical bovine thrombin (Thrombin-MI; King Pharmaceuticals, Bristol, TN, USA) is marketed in the United States as an aid to haemostasis for topical therapy of accessible minor bleeding from capillaries and small venules. Fibrin sealant [Tisseel VH (Baxter), consisting of human thrombin, fibrinogen concentrate and bovine aprotinin] is indicated as an adjunct to haemostasis in certain surgical situations, but it is not effective for the treatment of massive and brisk arterial bleeding. Fibrin sealants have been used with good results as adjunctive therapy for dental surgery in persons with haemophilia or VWD [237,293]. Topical collagen sponges are also approved for control of bleeding wounds [294]. Other topical agents approved for limited indications include Coseal (Baxter), BioGlue (CryoLife, Inc., Kennesaw, GA, USA) and QuikClot (Z-Medica Corporation, Wallingford, CT, USA); however, no reports of their use in treating VWD could be found. QuikClot, containing the mineral zeolite, was approved recently by the FDA for use with compression dressings for control of external traumatic bleeding in the prehospital setting (e.g. on the battlefield). The added benefit of topical agents – when used with single or combination therapies, including antifibrinolytic drugs, desmopressin and VWF/FVIII concentrate – is unproven. The topical use of plasma-derived bovine or human proteins imparts a theoretical risk of disease transmission and of potential allergic and other immune reactions. The use of fibrin sealants in addition to drugs, concentrates or both may be viewed

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as optional adjunctive therapy for dental surgery and for cases in which surface wound bleeding continues despite combined therapy with drugs and concentrates. The safety of these topical agents in therapy for VWD remains to be demonstrated.

Other issues in medical management
All persons with significant bleeding symptoms related to VWD are likely to require human blood product administration and should receive immunizations for hepatitis A and B as recommended for individuals with haemophilia [295]. Persons with VWD should be counselled to avoid aspirin, NSAIDs and other platelet-inhibiting drugs [296–298].

Treatment of AVWS
In an international registry of 189 cases of AVWS, desmopressin produced clinical and laboratory improvement in one-third of cases, although this effect was often short lived [114]. If FVIII activity and the PTT were abnormal, a good desmopressin response was less common than in hereditary VWD and was often brief. In the international registry series, most patients who had AVWS also received VWF/FVIII concentrates; the extent and duration of response varied. Therefore, VWF:RCo and FVIII levels must be measured preinfusion and postinfusion of desmopressin or VWF/FVIII concentrates in patients with AVWS to determine the extent and duration of response and to guide subsequent dosage and dosing intervals [114,152].

In patients who had a previous inadequate response to desmopressin and VWF/FVIII concentrates, i.v. immunoglobulin G (IGIV), 1 g kg\(^{-1}\) daily for 2 days, given alone was effective in controlling bleeding and raising VWF:RCo activity for 3 weeks in all eight patients who had excessive bleeding and an IgG monoclonal gammopathy of uncertain significance (MGUS) [299]. In the international registry series, one-third of the 63 patients treated with high-dose IGIV had a good response [114]. The underlying diagnoses of the responders were lymphoproliferative disorders (including MGUS), solid tumours and autoimmune diseases. An anti-VWF antibody could be demonstrated in vitro in about two-thirds of those responders. High-dose IGIV therapy in the setting of AVWS is an off-label use but should be considered when desmopressin and VWF/FVIII concentrate therapy fail to control bleeding symptoms adequately [300–302]. Some patients with immune-mediated AVWS have responded to plasmapheresis, corticosteroids and immunosuppressive agents [114]. Because many patients in the international registry series received multiple therapeutic modalities, the independent contribution of each therapy to clinical improvement was unclear.

When all other therapeutic modalities fail to control bleeding adequately, the infusion of recombinant activated factor VII (FVIIa) may be considered, but this agent should be used with caution. Little experience has been reported for its use in treating VWD. A recent report described acute myocardial infarction immediately after the second dose of 90 μg kg\(^{-1}\) in a 50-year-old man who had hereditary type 2A VWD, gastrointestinal tract bleeding and several risk factors for, but no history of, coronary artery disease [303].

Cardiac valvular diseases Congenital or acquired heart disease has been associated with AVWS [114,116,304]. Elevated shear stress around a stenotic valve or septal defect may promote the proteolysis and depletion of high-molecular-weight VWF multimers [131]. Patients who had associated aortic stenosis or other cardiac valvular disorders infrequently responded to any of the therapies described above [114,119]. After surgical correction of the cardiac defect, the multimer pattern has improved at least transiently in most patients studied [116,119,304]. Administration of VWF/FVIII concentrate immediately preoperatively should be considered for patients who demonstrate transient improvement in VWF activity with a test dose.

Angiodysplasia Bleeding from gastrointestinal angiodysplasia has been reported in persons with AVWS [305] as well as in persons with various types of congenital VWD. For example, bleeding from angiodysplasia is a classic presentation of AVWS associated with aortic stenosis [119,306] and is often resistant to medical therapy, requiring surgical correction of the valve defect to ameliorate bleeding symptoms. In the absence of a correctable underlying aetiology of angiodysplasia and bleeding associated with AVWS or congenital VWD, management of the condition can be challenging, as no single treatment modality is successful in all cases [307].

Thrombocytosis Thrombocytosis, especially in persons with essential thrombocythaemia, is associated with a relative reduction in the proportion of high-molecular-weight multimers [122]. Although the relation of this abnormality to bleeding is inconsistent, treatment is aimed at reduction of the platelet count.
Hypothyroidism  In contrast to the above syndromes, AVWS that occurs in hypothyroidism is caused by decreased synthesis, and the VWF multimer patterns are normal [308,309]. A minority of patients with hypothyroidism have VWF levels below normal, and not all who have low VWF levels have bleeding symptoms. The decrease in VWF is corrected by thyroid hormone replacement [124,309].

Management of menorrhagia in women with VWD
Menorrhagia is often the primary bleeding symptom in women with VWD [87,310,311]. Menorrhagia, however, may be a sign of a gynaecological disorder rather than VWD [312]. Therefore, a full gynaecological evaluation is required before therapy is initiated [312].

Medical therapies that have been described to control menorrhagia in women with VWD include combined oral contraceptives, tranexamic acid, desmopressin and, most recently, the levonorgestrel-releasing intrauterine system (Table 17). Data regarding the effectiveness of these therapies are limited. The only published randomized-clinical trial of desmopressin for menorrhagia was small and failed to demonstrate efficacy compared with placebo [313]. The available data show no evidence that desmopressin is more effective than other therapies used to treat menorrhagia [314]. Depending on the woman's age, underlying gynaecological condition and reproductive plans, any of the therapies demonstrated to be effective for the treatment of menorrhagia in women without VWD may be suitable, with the exception of NSAIDs, which decrease platelet function and systemic haemostasis [315]. In one retrospective review of 36 adolescent girls with VWD and menorrhagia, treatment using oral contraceptive pills or intranasal desmopressin were equally efficacious [316].

In adolescent or adult women who do not desire pregnancy, but may desire future child-bearing, the first choice of therapy should be combined oral contraceptives. Combined oral contraceptives contain a synthetic oestrogen (ethinyl estradiol) and a progestin [317]. The progestin prevents ovulation, and the synthetic oestrogen prevents breakthrough bleeding [318]. A majority of studies have found that combined oral contraceptives increase fibrinogen, prothrombin, FVII, FVIII and/or VWF [319–321] and, consequently, promote haemostasis. It is not known whether the increase in coagulation factors associated with combined oral contraceptives contributes to the clinical response, but combined oral contraceptives do reduce menstrual blood loss [322] and increase haemoglobin concentrations in women with anaemia [323–325]. Combined oral contraceptives...
tives, used by millions of women for prolonged periods of time, have been proven to be safe for long-term use [326] except in women with thrombophilia [318]. Although no formal studies of the effects of the contraceptive patch on haemostasis have been performed, the patch likely has effects similar to those of combined oral contraceptives [327].

For a woman who has VWD and would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy should be the levonorgestrel-releasing intrauterine system. The levonorgestrel-releasing intrauterine system is a progestin-impregnated intrauterine device that is believed to reduce menstrual blood loss by opposing oestrogen-induced growth of the endometrium or lining of the uterus [328].

Women who do not respond to hormonal therapy and are being considered for treatment with desmopressin or VWF concentrate should be referred to a haemophilia treatment centre or to a haematologist who has expertise in haemostasis. Treatments specific for VWD (such as desmopressin or VWF concentrate) or antifibrinolytic therapy, although they have not been proven to be effective for menorrhagia, may be tried.

In addition to medical therapies, surgical therapies have been used to treat menorrhagia in women with VWD. Dilation and curettage (D&C), while occasionally necessary to diagnose intrauterine pathology, is not effective in controlling heavy menstrual bleeding [329]. In two cases reported by Greer et al. [329] and two cases reported by Kadir et al. [330], D&C resulted in further blood loss. Endometrial ablation, however, reduced menstrual blood loss in seven of seven women who had VWD [331]. Three of these seven women ultimately required hysterectomy, compared with the 12–34% of women without VWD who usually require hysterectomy [332–336]. Women with VWD and who undergo hysterectomy may be at greater risk of peripherative bleeding complications than other women, and bleeding may occur despite prophylactic therapy [134,311]. Hysterectomy carries the risk of bleeding complications, but women who require the operation should not be deprived of its benefits. Because menorrhagia is often the primary bleeding symptom experienced by a woman who has VWD, hysterectomy offers the possibility of the elimination of menorrhagia bleeding symptoms and improved quality of life [336–338].

**Haemorrhagic ovarian cysts**

Multiple case reports describe women who have VWD and have experienced haemorrhagic ovarian cysts [329,339–344]. Silwer [134], for example, reported that nine of 136 women (6.8%) who had VWD experienced this problem. Ovulation is not normally accompanied by any clinically significant bleeding, but in a woman who has a congenital bleeding disorder such as VWD, the potential exists for bleeding into the peritoneal cavity or bleeding into the residual follicle, resulting in a haemorrhagic ovarian cyst [343] or retroperitoneal haematoma [329]. Acute treatment of haemorrhagic ovarian cysts with surgical therapy, tranexamic acid and factor replacement has been reported [329,342,343]. Oral contraceptives have been used to prevent recurrences [340,341,343].

**Pregnancy**

Few options are available for the management of menorrhagia or recurrent haemorrhagic ovarian cysts in women who have VWD and desire pregnancy. Although data are limited to case reports, desmopressin, antifibrinolytics or VWF concentrate may be tried [339].

Ideally, planning for pregnancy begins before conception. Women who have VWD and are contemplating a pregnancy should be aware that they may be at increased risk of bleeding complications during pregnancy [345] and are definitely at increased risk of postpartum haemorrhage [139]. Before conception or during pregnancy, women should be offered the opportunity to speak with a genetic counsellor regarding the inheritance of VWD [346] and with a paediatric haematologist regarding the evaluation of the infant after delivery.

Women who have type 1, type 2 or type 3 VWD and have FVIII levels <50 IU dL\(^{-1}\), VWF:RCo <50 IU dL\(^{-1}\) or a history of severe bleeding should be referred for prenatal care and delivery to a centre that, in addition to specialists in high-risk obstetrics, has a haemophilia treatment centre, a haematologist with expertise in haemostasis or both. Laboratory, pharmacy and blood bank support is essential. Before any invasive procedure, such as chorionic villus sampling, amniocentesis or cervical cerclage, women with VWD should have laboratory assays for FVIII and VWF:RCo to receive appropriate prophylaxis [346,347]. FVIII and VWF:RCo levels should be obtained in the third trimester of pregnancy to facilitate planning for the delivery [347]. Before delivery, all women with VWD should meet with an anaesthesiologist to plan for the possible need for the administration of haemostatic agents or alternatives, if necessary, for regional anaesthesia at the time of delivery [346]. A pregnant woman carrying a baby at
risk for type 3 VWD or severe forms of types 1 or 2 VWD should be referred to a paediatric haematologist for counselling regarding neonatal testing and potential perinatal bleeding complications in affected infants [87,345,348].

Data are limited on the use of desmopressin for VWD in pregnancy. Mannucci [349] reported using desmopressin for prophylaxis before procedures in 31 pregnant women ‘without mishap’, but specific data were not provided. Desmopressin, in the lower doses used to treat diabetes insipidus, however, is generally thought to be safe for mother and foetus. In doses used to treat diabetes insipidus, no adverse foetal effects were not found to be teratogenic in rabbits [357]. In cases of its use during pregnancy, no adverse foetal effects have been reported [358].

Miscarriage and bleeding during pregnancy In the general population, miscarriage is common, and 12–13.5% of diagnosed pregnancies result in spontaneous abortion [359,360]. Although detailed data were not provided, in a study of 182 women who had severe VWD, Lak et al. [87] reported that miscarriage was no more frequent than in the general population. Other studies, however, have found a higher incidence of miscarriage among women with VWD than in controls [139] or in the background rate [339,345].

Bleeding complications during pregnancy other than miscarriage have been reported [329,339,361–363]. Kadir et al. [345] found that 33% of women who had VWD bled during their first trimester.

Childbirth Table 18 summarizes nine case series reporting pregnancy outcomes in women with VWD, including rates of miscarriage, peripartum prophylaxis, postpartum haemorrhage and perineal haematoma. Prophylaxis included cryoprecipitate, fresh-frozen plasma, desmopressin and factor replacement.

No large prospective studies correlate VWF:RCo and FVIII levels with the risk of bleeding at the time of childbirth, but the opinion of experts is that VWF:RCo and FVIII levels of 50 IU dL\(^{-1}\) should be achieved before delivery [329] and maintained for at least 3–5 days afterward [9,212,329,345–347]. There is no consensus on levels of VWF:RCo and FVIII that are safe for regional anaesthesia [364], but if VWF:RCo and FVIII levels are 50 IU dL\(^{-1}\) or higher and the coagulation screen is normal, regional anaesthesia may be considered safe [345].

Desmopressin may be used to raise factor levels in responders, but care must be taken in its administration at the time of childbirth. Women commonly receive 1–2 L or more of fluid at the time of a vaginal delivery and 2–3 L or more at the time of caesarean delivery. Fluids containing oxytocin, which also causes fluid retention, combined with desmopressin may result in fluid retention and life-threatening hyponatraemia. Chediak and colleagues [363] reported complications of fluid retention in two women who received desmopressin at the time of childbirth. One woman who received three doses 18 h apart developed severe hyponatraemia (sodium level of 108 mEq L\(^{-1}\)) and experienced grand mal seizures.

Because NSAIDs, commonly prescribed for pain after childbirth, may decrease platelet function and systemic haemostasis [315], alternative analgesics should be considered.

Postpartum haemorrhage Postpartum haemorrhage is an anticipated problem among women with VWD. By the end of gestation, an estimated 10–20% of a woman’s blood volume, or at least 750 mL min\(^{-1}\), flows through the uterus [365]. After delivery of the infant and placenta, the uterus must contract, and the uterine vasculature must constrict to prevent exsanguination [366]. Failure of the uterus to contract is the single most important cause of postpartum haemorrhage [366]. Nonetheless, women with VWD have a greater risk of postpartum haemorrhage than controls [134,139,367]. Multiple case series document an increased incidence of postpartum haemorrhage in women with VWD (Table 18).

Perineal haematoma, a rare complication of vaginal birth, occurs with some frequency in women with VWD. Greer et al. [329] reported one haematoma in 13 vaginal deliveries, and Kadir and colleagues [345] reported three haematomas in 49 vaginal deliveries. This is a relatively high frequency compared with a rate of only 2.2 haematomas per 1000 vaginal births in a cohort of 26 187 spontaneous or operative vaginal deliveries [368].

In women with VWD, vaginal bleeding is frequently reported to occur more than 2–3 weeks postpartum. The duration of bleeding after delivery in a normal patient is a median of 21–27 days [369–371].
Table 18. Pregnancies in women with VWD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Miscarriage</th>
<th>Prophylaxis</th>
<th>Postpartum haemorrhage</th>
<th>Perineal haematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burlingame et al. [361]</td>
<td>5 pregnancies in 2 women</td>
<td>None</td>
<td>FVIII/VWF concentrates for 1/5</td>
<td>1/5 (20%)</td>
<td>None</td>
</tr>
<tr>
<td>Lak et al. [87]</td>
<td>100 women with type 3 VWD and had delivered at least 1 child</td>
<td>Rate not 'higher than... the general Iranian population'</td>
<td>FFP, cryo, FVIII/VWF concentrates for 2/2</td>
<td>15/100 (15%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Caliezi et al. [362]</td>
<td>2 pregnancies in 1 woman with type 3 VWD</td>
<td>None</td>
<td>FVIII/VWF concentrates for 2/2</td>
<td>10/54 (18%)</td>
<td>None</td>
</tr>
<tr>
<td>Kadir et al. [345]</td>
<td>84 pregnancies in 31 women</td>
<td>18 of 72 pregnancies not terminated</td>
<td>10/54 with 'no bleeding complications'</td>
<td>3/54</td>
<td></td>
</tr>
<tr>
<td>Foster [339]</td>
<td>69 pregnancies in 31 women with VWD unresponsive to DDAVP</td>
<td>15 of 68 pregnancies not terminated</td>
<td>25/55 (46%) of those for whom data were available; FVII/VWF concentrates (9); cryo (8); FFP (1)</td>
<td>In women who had type 2A, 2B or 3 VWD, 6/18 (33%) who were treated; 3/4 (75%) who were not treated</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ramsahoye et al. [376]</td>
<td>24 pregnancies in 13 women</td>
<td>None reported (1 foetal demise at 38 weeks)</td>
<td>5 caesarean deliveries: cryo for 2/5; FVIII/VWF concentrate (Haemate-P(^2)) for 2/5; DDAVP for 1/5; 19 vaginal deliveries: cryo for 3/19; FVIII/VWF concentrate (Haemate-P(^2); NHS 8Y) for 2/19</td>
<td>3/24 (12.5%) primary(^<em>); 6/24 (25%) secondary(^</em>); 2/6 secondary(^*) had been treated</td>
<td>None</td>
</tr>
<tr>
<td>Greer et al. [329]</td>
<td>14 deliveries in 7 women with VWD</td>
<td>Not reported</td>
<td>Cryo (9)</td>
<td>5/9 who were treated (1 primary(^<em>), 3 secondary(^</em>), 1 both); 2/5 who were not treated (2 primary(^*))</td>
<td>1/14</td>
</tr>
<tr>
<td>Chediak et al. [363]</td>
<td>10 pregnancies in 6 women with VWD</td>
<td>3/10 pregnancies</td>
<td>Cryo for 5/7 deliveries; DDAVP for 2/7 deliveries</td>
<td>4/5 'massive'</td>
<td>1 had lumbar haematoma's</td>
</tr>
<tr>
<td>Conti et al. [390]</td>
<td>5 deliveries in 5 women with VWD</td>
<td>None</td>
<td>None</td>
<td>2/5 'late'</td>
<td>None</td>
</tr>
</tbody>
</table>

Cryo, cryoprecipitate; DDAVP, desmopressin; FFP, fresh-frozen plasma; FVIII/VWF, factor VIII/von Willebrand factor concentrate; NHS 8Y, National Health Service (UK) FVIII/VWF concentrate (8Y); VWD, von Willebrand disease.

\(^*\) Primary, postpartum haemorrhage within the first 24 h after delivery.

\(^*\) Secondary, postpartum haemorrhage after 24 h after delivery.

\(^2\) Haemate-P is the European equivalent of Humate-P.
However, the VWF levels that are elevated during pregnancy return to baseline within 7–21 days [372,373], predisposing women with VWD to delayed postpartum haemorrhage. In the absence of a bleeding disorder, delayed or secondary postpartum haemorrhage is rare and occurs after <1% of deliveries [374,375]. In contrast, 20–25% of women with VWD had delayed postpartum haemorrhage, making delayed postpartum haemorrhage 15–20 times more common among these women than in normal subjects [345,376].

Among the published series of cases of women who were pregnant and had VWD (Table 18), multiple cases of postpartum haemorrhage occurred despite prophylaxis. The mean ± SD time of presentation of postpartum haemorrhage in women with VWD was estimated to be 15.7 ± 5.2 days after delivery [377]. The implication is that women with VWD may require frequent evaluation — and possibly prophylaxis — for 2 weeks or more postpartum. Weekly contact with these women is recommended during the postpartum period [347].

Management recommendations

The recommendations are graded according to criteria described in Table 1. Management Recommendations IV–X summarize the Panel’s patient management recommendations. Evidence Tables 6–13 are provided in the full online document [10] for recommendations given a grade of B and having two or more references.

Management Recommendations IV

IV. Testing Before Treatment

A. Before treatment, all persons suspected of having von Willebrand disease (VWD) should have a laboratory-confirmed diagnosis of type and severity of VWD. This recommendation does not preclude treatment that may be indicated for urgent or emergency situations, despite the absence of confirmatory laboratory data.

Grade C, level IV [87,133–136,148,394,395]

B. Persons who do not have a definite diagnosis of VWD but who have von Willebrand factor ristocetin cofactor activity (VWF:RCo) levels of 30–50 IU dL−1 and have a bleeding phenotype may merit treatment or prophylaxis of bleeding in certain clinical situations.

Grade B, level III [191]

C. Persons with activity levels of VWF:RCo higher than 10 IU dL−1 and factor VIII (FVIII) higher than 20 IU dL−1 should undergo a trial of desmopressin while in a nonbleeding state. Persons with levels below these thresholds are less likely to demonstrate clinical or laboratory responses to desmopressin, but a desmopressin trial should still be considered in these individuals.

Grade B, level IIa [101,218,220,221,224]

See Evidence Table 6 [10] for additional information and detail.

Management Recommendations V

V. General Management

A. Treatment of persons who have von Willebrand disease (VWD) is aimed at cessation of bleeding or prophylaxis for surgical procedures.

Grade C, level IV [1,7,9]

B. Continued bleeding, despite adequately replaced von Willebrand factor ristocetin cofactor (VWF:RCo) and factor VIII (FVIII) activity levels, requires evaluation of the person for other bleeding aetiologies, including anatomic.

Grade C, level IV

C. Long-term prophylaxis is currently under investigation in an international cooperative study, and the long-term risks and benefits should be considered carefully.

Grade C, level IV [208,209]

D. Individuals who are more than 2 years old, have VWD, and have not already been vaccinated should be immunized against hepatitis A and B.

Grade C, level IV [295]

E. Persons with VWD should have the opportunity to talk to a knowledgeable genetic counselor.

Grade C, level IV [346]

F. At diagnosis, persons with VWD should be counseled to avoid aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and other platelet-inhibiting drugs.

Grade C, level IV [296–298]

G. Restriction of fluids to maintenance levels should be considered in persons receiving desmopressin (especially for young children and in surgical settings) to avoid the occurrence of hyponatraemia and seizures.

Grade C, level IV [258–260]
Management Recommendations VI

VI. Treatment of Minor Bleeding and Prophylaxis for Minor Surgery

A. Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with intravenous or nasal desmopressin, if appropriate, based on trial testing.

Grade B, level IIa [220,223,227,229,238]
See Evidence Table 7 [10] for additional information and detail.

B. If elevation of von Willebrand factor (VWF) is necessary and response to desmopressin is inadequate, VWF concentrate should be used, with dosing primarily based on von Willebrand factor ristocetin cofactor activity (VWF:RCo) units and secondarily on factor VIII (FVIII) units.

Grade C, level IV [239,250]

C. For prophylaxis for minor surgery, initial treatment should be expected to achieve VWF:RCo and FVIII activity levels of at least 30 IU dL⁻¹ and preferably higher than 50 IU dL⁻¹.

Grade B, level III [220,223,237,239]
See Evidence Table 8 [10] for additional information and detail.

D. For minor surgery, VWF:RCo and FVIII activity levels of at least 30 IU dL⁻¹ and preferably higher than 50 IU dL⁻¹ should be maintained for 1–5 days.

Grade B, level III [239,245,246,253]
See Evidence Table 9 [10] for additional information and detail.

E. For persons with VWD, management of minor bleeding (e.g. epistaxis, simple dental extraction or menorrhagia) with desmopressin and proper fluid restriction can be performed without laboratory monitoring unless desmopressin is used more than three times within 72 h.

Grade C, level IV [257,316]

F. For persons with mild to moderate von Willebrand disease (VWD), antifibrinolytics combined with desmopressin are generally effective for oral surgery. VWF concentrate should be available for persons who cannot receive desmopressin or who bleed excessively despite this combined therapy.

Grade B, level IIb [220,225,229,237–240]
See Evidence Table 10 [10] for additional information and detail.

G. Topical agents, such as fibrin sealant or bovine thrombin, may be useful adjuncts for oral surgery in persons with VWD. Careful attention to haemostasis of an extraction socket and to suturing of sockets is also important in oral surgery in persons with VWD.

Grade C, level IV [237,293]

Management Recommendations VII

VII. Treatment of Major Bleeding and Prophylaxis for Major Surgery

A. All treatment plans should be based on objective laboratory determination of response of von Willebrand factor ristocetin cofactor (VWF:RCo) and factor VIII (FVIII) activity levels to desmopressin or to von Willebrand factor (VWF) concentrate infusion.

Grade B, level IIb [133,221,239,242–244,246–253,288,403]
See Evidence Tables 11 and 12 [10] for additional information and detail.

B. Whenever possible, all major surgical procedures and bleeding events should be treated in hospitals with around-the-clock laboratory capability and with clinical monitoring by a team that includes a haematologist and a surgeon skilled in the management of bleeding disorders.

Grade C, level IV

C. For severe bleeding (e.g. intracranial, retroperitoneal) or for prophylaxis during major surgery, initial target VWF:RCo and FVIII activity levels should be at least 100 IU dL⁻¹. Subsequent dosing should maintain VWF:RCo and FVIII levels above a trough of 50 IU dL⁻¹ for at least 7–10 days.

Grade B, level III [239,246,248–253,288,403]
See Evidence Table 12 [10] for additional information and detail.

D. To decrease risk of perioperative thrombosis, VWF:RCo levels should not exceed 200 IU dL⁻¹, and FVIII activity should not exceed 250 IU dL⁻¹.

Grade C, level IV [277–279]

E. For major surgical procedures in selected patients with type 3 von Willebrand disease or acquired von Willebrand syndrome who are at risk for poor VWF recovery because of inhibitors, a preoperative trial infusion of VWF concentrate with pharmacokinetic laboratory monitoring should be considered.

Grade C, level IV
Management Recommendations VIII

VIII. Management of Menorrhagia and Haemorrhagic Ovarian Cysts in Women With VWD

A. Women who have menorrhagia or abnormal vaginal bleeding should have a full gynaecologic evaluation before therapy.  
Grade C, level IV [312]

B. In an adolescent or adult woman who does not desire pregnancy but may desire future childbearing, the first choice of therapy for menorrhagia should be combined oral contraceptives.  
Grade B, level III [339]

C. In an adolescent or adult woman who does not desire pregnancy but may desire future childbearing, the first choice of therapy to prevent haemorrhagic ovarian cysts should be combined oral contraceptives.  
Grade C, level IV [340,341,343]

D. If a woman would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy for menorrhagia should be the levonorgestrel intrauterine system.  
Grade B, level IIb [404]

E. For a woman who desires pregnancy, desmopressin, antifibrinolytics, or VWF concentrate may be tried to control menorrhagia.  
Grade C, level IV [339]

F. Dilation and curettage is not usually effective to manage excessive uterine bleeding in women with VWD.  
Grade C, level IV [329,330]

Management Recommendations IX

IX. Management of Pregnancy and Childbirth in Women With VWD

A. Women planning for pregnancy should have, before conception, an evaluation with a haematologist and high-risk obstetrician, both of whom are skilled in the management of von Willebrand disease (VWD).  
Grade C, level IV [346]

B. Women with type 1, type 2, or type 3 VWD, with factor VIII (FVIII) or von Willebrand factor ristocetin cofactor (VWF:RCo) activity levels <50 IU dL\(^{-1}\) or a history of severe bleeding:  
1. Should be referred to a centre that has high-risk obstetrics capabilities and expertise in haemostasis for prenatal care, delivery, termination of pregnancy, or management of miscarriage.  
Grade C, level IV

2. Should receive prophylaxis with desmopressin or von Willebrand factor (VWF) concentrate before invasive procedures.  
Grade C, level IV [346,347]

3. Should achieve VWF:RCo and FVIII levels of at least 50 IU dL\(^{-1}\) before delivery and maintain those levels for at least 3–5 days afterward.  
Grade C, level IV [9,212,339,345,347]

C. If VWF:RCo and FVIII levels can be monitored and maintained above 50 IU dL\(^{-1}\) during labor and delivery, and no other coagulation defects are present, then regional anaesthesia may be considered.  
Grade C, level IV [345]

D. Because coagulation factors return to prepregnancy levels within 14–21 days after delivery, health care providers should be in close contact with women during the postpartum period.  
Grade C, level IV [347]

Management Recommendations X

X. Acquired von Willebrand Syndrome

A. Individuals who have acquired von Willebrand syndrome (AVWS) and who require surgery should be considered for a pharmacokinetic trial of therapy with desmopressin and/or von Willebrand factor (VWF) concentrate, with monitoring of von Willebrand factor ristocetin cofactor (VWF:RCo) and factor VIII (FVIII), to evaluate for possible accelerated clearance of VWF.  
Grade C, level IV [114,152]

B. For persons who have AVWS and who bleed excessively despite therapy with desmopressin and VWF concentrate, treatment with high-dose intravenous immunoglobulin (IGIV) should be considered, especially in IgG isotype monoclonal gammopathy of uncertain significance (MGUS). (See discussion of this use, not approved by the US Food and Drug Administration, in the section Treatment of AVWS.)  
Grade B, level IIa [114,299–302]

See Evidence Table 13 [10] for additional information and detail.
Opportunities and needs in VWD research, training and practice

Many recommendations in this guideline are based on relatively limited evidence, thus underscoring the need for further research. Some of these opportunities are discussed below.

Pathophysiology and classification of VWD

Determinants of VWF level and bleeding risk The risk of bleeding in persons with VWD depends on the level of functional VWF and on many other factors that are poorly understood. The plasma level of VWF can be influenced by mutations within or near the VWF gene. In addition, VWF levels depend on ABO blood type [45], possibly on the Secretor locus [111], and on hormonal status and stress, as discussed in The VWF Protein and its Functions In Vivo. Relatively few of the genetic and non-genetic determinants of VWF level have been characterized, and how they interact is not known. In addition, little quantitative information is available on the risk of specific bleeding symptoms as a function of the level of VWF in plasma. This information would be particularly useful for the management of patients who have VWF levels in the range of 30–50 IU dL\(^{-1}\), for whom the risk of medically significant bleeding is not well defined.

VWF level in plasma alone does not account for the observed variation in bleeding symptoms, and recent studies are starting to uncover some of the underlying reasons. For example, persons who have both low VWF and defects in platelet aggregation have more severe bleeding [378]. Increased bleeding has also been associated with specific DNA markers for platelet membrane proteins [379]. It is likely that multiple haemostatic risk factors interact with VWF level in plasma to determine the likelihood of bleeding or thrombosis. Understanding these interactions and incorporating them into clinical practice will require additional basic, clinical, and epidemiological research.

Heterogeneity of type 1 VWD Partial quantitative deficiency of VWF can be caused by several mechanisms, as discussed in the section Classification of VWD Subtypes. Some persons have dominant VWF mutations that either decrease the secretion of VWF multimers or accelerate their clearance from the circulation. The prevalence of increased clearance as a cause of type 1 VWD is not known. Whether these different disease mechanisms correlate with distinct clinical features, including response to specific treatments, also is not known. Because type 1 VWD is the most common form of VWD, answers to these questions may have important consequences for medical practice.

Heterogeneity of type 2 VWD The concentration of haemostatically effective large VWF multimers can be selectively decreased by accelerated proteolysis or by various defects in multimer assembly [51]. These variants now are grouped together as type 2A VWD, but further subdivision of this category would be justifiable if specific mechanisms of disease were associated with different clinical symptoms or responses to therapy.

Most persons with type 2M VWD have been identified by finding a profound defect in ristocetin-induced binding to platelets associated with a normal VWF multimer pattern [57,69,74]. Defects in binding to collagen or other connective tissue elements could cause a similar bleeding phenotype, but the VWF:RCo assay is insensitive to such defects [75]. Collagen-binding abnormalities can be detected by the VWF:CB assays, but those assays are not used widely in the United States. The prevalence and medical importance of collagen-binding defects in type 2M VWD deserve further study.

Diagnosis and evaluation

Assessment of bleeding signs and symptoms The initial evaluation of patients for a medically important bleeding disorder can be difficult because mild bleeding is common in the healthy population. Specific symptoms have been assessed for clinical relevance in retrospective studies, and some appear to discriminate between healthy controls and persons with diagnosed bleeding disorders (Table 9 and Fig. 3). However, the utility of these questions must be established prospectively for less highly selected persons.

Quality and availability of laboratory testing Reliable testing for VWF:Ag and FVIII is widely available, but VWF:RCo, RIPA and VWF multimer analysis are much more variable in their performance characteristics and can be difficult to obtain. Also, tests of VWF:FVIIIIB are offered by few laboratories. More robust methods for assessing VWF function and multimer structure must be developed for routine use in the diagnosis of VWD. In addition, the sensitivity and specificity of test ratios such as VWF:RCo/ VWF:Ag should be established for identifying the qualitative defects that characterize type 2A and type 2M VWD. Criteria should be established for VWF
multimer analysis to distinguish a significant decrease in large multimers (in types 2A and 2B VWD) from a substantially normal multimer distribution (in types 1, 2M and 2N VWD).

**VWF gene sequencing** Mutations that cause many types of VWD can be identified by sequencing the VWF gene in DNA samples from patients [24]. The locations of mutations appear to correlate well with some disease phenotypes, suggesting that DNA sequencing could be a useful diagnostic method in VWD. With appropriate study and experience, DNA sequencing may become economical and feasible for routine use. In addition, the widespread application of VWF gene sequencing would provide invaluable information about the prevalence of VWF mutations as a function of VWF level, the strength of the relationship between VWF genotype and VWD phenotype, the penetrance of specific mutations, and the biochemical mechanisms that cause VWD. This knowledge would also be an outstanding resource for the identification and characterization of other factors that modify bleeding symptoms in VWD.

**Management of VWD**

Many of the standard treatments for VWD have limited experimental support. For example, the intensity and duration of therapy necessary to control bleeding have not been established for many clinical situations and often have been extrapolated from anecdotal experience in haemophilia. The indications for prophylaxis of bleeding are not well defined. These issues should be addressed by appropriate clinical studies.

**Desmopressin** Many persons with VWD respond to desmopressin with a clinically useful rise in VWF and FVIII, but the likelihood of a good outcome depends on the type of VWD and the underlying biochemical mechanism of disease. In type 1 VWD, persons who have accelerated clearance of plasma VWF may have a transient response to desmopressin [43,225]. Whether desmopressin should be used at all in persons with type 2B VWD is controversial [226,234,254,255,380–383]. In type 2N VWD, the baseline FVIII level may be a good predictor of the magnitude and duration of the FVIII response to desmopressin [79,224,228,384]. The drug is thought to be safe for use in pregnancy, but the published experience in this setting is limited [268,269]. Hypo- 

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Haemophilia (2008), 14, 171–232

Factor concentrates The available plasma-derived products that contain VWF also contain FVIII as part of the FVIII–VWF complex, and only two such products are currently licensed in the United States for treatment of VWD. When administered to patients with VWD, the infused FVIII may add to the endogenous FVIII production and cause markedly elevated FVIII levels that are much greater than the VWF levels achieved with treatment; these have been associated with thrombosis [212]. High FVIII levels can be avoided by adjusting the dose of product administered, but VWF levels then may be relatively low. Whether FVIII or VWF levels or both, should be used to monitor treatment with FVIII–VWF concentrates is unknown. Use of a pure VWF product in place of FVIII–VWF concentrates would avoid the disproportionate increase in FVIII. A pure VWF concentrate has been used in Europe [385] but is not currently available in the United States. Studies are needed to establish appropriate treatment and monitoring regimens for these products. In addition, prelicensure studies of recombinant VWF are needed to establish its safety, efficacy and role in the treatment of VWD. The licensing of other products containing both VWF and FVIII would also enhance therapeutic options.

Platelets Approximately 15% of the total VWF in blood is found within platelets, and platelet VWF appears to contribute to haemostasis. Although VWD patients who have abnormal or low platelet VWF have been described, there has been only limited exploration of the feasibility and utility of such testing, in part because of limitations of practical methods. Clinically, platelet transfusions have been reported to stop bleeding in some patients with VWD who were not helped by transfusion of FVIII–VWF concentrates [289,290]. The efficacy and appropriate use of platelet transfusions in persons with VWD or AVWS need to be established.

Antifibrinolytics Tranexamic acid and aminocaproic acid have been used alone or as adjunctive therapy to treat bleeding in VWD. The safety, efficacy, and optimal dosing of these agents in VWD should be established by suitable clinical studies. In addition, the availability of orally administered tranexamic acid would broaden the therapeutic options for antifibrinolytic therapy.
Gene therapy of VWD

Severe type 3 VWD potentially can be treated with gene therapy. The gene for VWF is larger than could easily be introduced into many vectors, but gutless adenoviral vectors could easily accommodate a gene the size of VWF (8.5 kb). The prevalence of type 3 VWD and its clinical symptoms, however, does not place it in a high-priority category for gene therapy trials. Point mutation repair initially was an exciting approach for VWD [386,387], but follow-up studies have not achieved the same rate of success in vitro [388,389].

Issues specific to women

VWF is particularly important for haemostasis during menses and at childbirth. Consequently, women are affected disproportionately by having VWD, especially during their child-bearing years.

Menorrhagia The incidence of menorrhagia appears to vary inversely with VWF level, independent of whether women meet criteria for having VWD [47]. Because menorrhagia is so common, even a small reduction in its severity could have important implications for women’s health. As discussed in the section Menorrhagia, several treatments have been used for menorrhagia associated with VWD, but their efficacy has not been demonstrated convincingly. Therefore, clinical studies would be useful to establish the effect of VWF level on menorrhagia and to evaluate specific treatments for women who have VWD or low plasma levels of VWF.

Labour and delivery Several small case series indicate that women who have VWD and VWF levels <50 IU dL⁻¹ at delivery have an increased incidence of immediate and delayed postpartum haemorrhage. These complications appear to be prevented by replacement therapy with FVIII–VWF concentrate before delivery and by either concentrate or desmopressin in the postpartum period [87,345,390]. How the risk of bleeding correlates with VWF level or FVIII level is not known, and the required intensity and duration of therapy have not been established.

Training of specialists in haemostasis

In the United States, despite scientific progress in basic and clinical research in bleeding and thrombotic disorders, including VWD, there is a shortage of skilled clinicians and laboratorians with expertise in haemostasis [391]. Training opportunities need to be developed and expanded for haemostasis specialists. Recent clinical training opportunities include a new NHLBI initiative for training in non-malignant haematology [392] and a recent clinical fellowship initiative from the National Hemophilia Foundation [393]. Recognition of haemostasis as a bona fide clinical and laboratory subspecialty in the United States could enhance entry into the field.

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Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

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The aims of severe perioperative bleeding management are three-fold. First, preoperative identification by anamnesis and laboratory testing of those patients for whom the perioperative bleeding risk may be increased. Second, implementation of strategies for correcting preoperative anaemia and stabilisation of the macro- and microcirculations in order to optimise the patient’s tolerance to bleeding. Third, targeted procoagulant interventions to reduce the amount of bleeding, morbidity, mortality and costs. The purpose of these guidelines is to provide an overview of current knowledge on the subject with an assessment of the quality of the evidence in order to allow anaesthetists throughout Europe to integrate this knowledge into daily patient care wherever possible. The Guidelines Committee of the European Society of Anaesthesiology (ESA) formed a task force with members of scientific subcommittees and individual expert members of the ESA. Electronic databases were searched without language restrictions from the year 2000 until 2012. These searches produced 20,664 abstracts. Relevant systematic reviews with meta-analyses, randomised controlled trials, cohort studies, case-control studies and cross-sectional surveys were selected. At the suggestion of the ESA Guideline Committee, the Scottish Intercollegiate Guidelines Network (SIGN) grading system was initially used to assess the level of evidence and to grade recommendations. During the process of guideline development, the official position of the ESA changed to favour the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. This report includes general recommendations as well as specific recommendations in various fields of surgical interventions. The final draft guideline was posted on the ESA website for four weeks and the link was sent to all ESA members. Comments were collated and the guidelines amended as appropriate. When the final draft was complete, the Guidelines Committee and ESA Board ratified the guidelines.

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### 1 ABBREVIATIONS

A5, A10 Amplitude at 5/10 min following clotting time
AAGBI Association of Anaesthetists of Great Britain and Ireland
ACS Acute coronary syndrome
ADP Adenosine diphosphate
ALI Acute lung injury
APA Anti-platelet agents
APCC Activated prothrombin complex concentrate
APTEM Thromboelastometry assay incorporating aprotinin and recombinant tissue factor as an activation enhancer
aPTT Activated partial thromboplastin time
AT Antithrombin
ATP Adenosine triphosphate
AVB Acute variceal bleeding
BART Blood conservation using antifibrinolytics in a randomised trial
BAT Bleeding assessment tool
CABG Coronary artery bypass graft
CADP Collagen and ADP (PFA-100 assay)
CCI Corrected count increment
CEPI Collagen and epinephrine (PFA-100 assay)
CFT Clot formation time (also called k time)
CI Confidence interval
CKD Chronic kidney disease
CLD Chronic liver disease
CMV Cytomegalovirus
COX Cyclo-oxygenase
CPA Cone and plate(let) analyser (Impact-R)
CPB Cardiopulmonary bypass
CT Clotting time
CVP Central venous pressure
DIC Disseminated intravascular coagulation
DPG Diphosphoglycerol
EACA e-aminocaproic acid
EMA European Medicines Agency
EXTEM Extrinsic thromboelastometry assay incorporating recombinant tissue factor as activation enhancer
FF Functional fibrinogen (assay)
FFP Fresh frozen plasma
FIBTEM Fibrinogen thromboelastometry assay, incorporating recombinant tissue factor as activation enhancer and cytochalasin D as platelet inhibitor
FNHTR Febrile non-haemolytic transfusion reactions
FVIII Factor VIII
FXa Factor Xa
FXIII Factor XIII
G Clot rigidity
GP Glycoprotein
Hb Haemoglobin
HBV Hepatitis B virus
HCV Hepatitis C virus
HELLP Haemolysis, elevated liver enzymes and low platelets
HEPTEM Thrombelastometry assay incorporating heparinase and ellagic acid as an activation enhancer
HES Hydroxyethyl starch
HIV Human immunodeficiency virus
HTLV Human T-cell lymphotropic virus
HTRs Haemolytic transfusion reactions
HV Hyperoxic ventilation
ICH Intracerebral haemorrhage
ICS Intraoperative cell salvage
ICT Intracardiac thrombi
ICU Intensive care unit
INR International normalised ratio
INTEM Intrinsic thromboelastometry assay incorporating ellagic acid as activation enhancer
LI30 Lysis index (% of clot strength remaining 30 min after CT)
LMWH Low molecular weight heparin
LTA Light transmittance aggregometry
LY30 Lysis index (% of clot strength remaining 30 min after MA)
MA Maximum amplitude
MBD Mild bleeding disorders
MCB Mucocutaneous bleeding
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>MCE</td>
<td>Maximum clot elasticity</td>
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<tr>
<td>MCF</td>
<td>Maximum clot firmness</td>
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<tr>
<td>MEA</td>
<td>Multiple electrode aggregometry (Multiplate)</td>
</tr>
<tr>
<td>ML</td>
<td>Maximum lysis</td>
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<tr>
<td>NATEM</td>
<td>Native thromboelastometry assay (no activation enhancement or additional modifications)</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Health and Clinical Excellence</td>
</tr>
<tr>
<td>NOA</td>
<td>New oral anticoagulant agent</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-selective, non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OLT</td>
<td>Orthotopic liver transplantation</td>
</tr>
<tr>
<td>PAI</td>
<td>Plasminogen activator inhibitor</td>
</tr>
<tr>
<td>pO2</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PEP</td>
<td>Pulmonary embolism prevention (trial)</td>
</tr>
<tr>
<td>PFA-100</td>
<td>Platelet function analyser</td>
</tr>
<tr>
<td>PPV</td>
<td>Pulse pressure variation</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>r</td>
<td>Reaction time</td>
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<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>RBD</td>
<td>Rare bleeding disorder</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Recombinant activated factor VII</td>
</tr>
<tr>
<td>ROTEM</td>
<td>Thromboelastometry</td>
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<tr>
<td>SBT</td>
<td>Skin bleeding time</td>
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<tr>
<td>ScvO2</td>
<td>Central venous oxygen saturation</td>
</tr>
<tr>
<td>SD</td>
<td>Solvent and detergent</td>
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<tr>
<td>SHOT</td>
<td>Serious hazards of transfusion</td>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<tr>
<td>SLT</td>
<td>Standard laboratory test</td>
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<tr>
<td>SPRINT</td>
<td>Systolic blood pressure intervention trial</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SVV</td>
<td>Stroke volume variation</td>
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<tr>
<td>TACO</td>
<td>Transfusion-associated circulatory overload</td>
</tr>
<tr>
<td>TAE</td>
<td>Transcatheter arterial embolisation</td>
</tr>
<tr>
<td>TA-GVHD</td>
<td>Transfusion-associated graft-versus-host disease</td>
</tr>
<tr>
<td>TEG</td>
<td>Thromboelastometry</td>
</tr>
<tr>
<td>TF</td>
<td>Tissue factor</td>
</tr>
<tr>
<td>THA</td>
<td>Total hip arthroplasty</td>
</tr>
<tr>
<td>TRALI</td>
<td>Transfusion-related acute lung injury</td>
</tr>
<tr>
<td>TRAP</td>
<td>Thrombin receptor activator peptide</td>
</tr>
<tr>
<td>TRICC</td>
<td>Transfusion requirements in critical care (trial)</td>
</tr>
<tr>
<td>TRIM</td>
<td>Transfusion-related immunomodulation</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>UGIB</td>
<td>Upper gastrointestinal bleeding</td>
</tr>
<tr>
<td>vCJD</td>
<td>Variant Creutzfeldt-Jacob disease</td>
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<tr>
<td>VKA</td>
<td>Vitamin K antagonist</td>
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<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
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<tr>
<td>VWD</td>
<td>Von Willebrand disease</td>
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<tr>
<td>VWF</td>
<td>Von Willebrand factor</td>
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2 SUMMARY: RECOMMENDATIONS, SUGGESTIONS AND STATEMENTS

Grade of recommendation shown in bold type (see Table 1)

Evaluation of coagulation status
We recommend the use of a structured patient interview or questionnaire before surgery or invasive procedures, which considers clinical and family bleeding history and detailed information on the patient’s medication. 1C

We recommend the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, PT and platelet count in elective surgery. 1C

We recommend the application of transfusion algorithms incorporating predefined intervention triggers to guide haemostatic intervention during intraoperative bleeding. 1B

We recommend the application of transfusion algorithms incorporating predefined intervention triggers based on point-of-care (POC) coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery. 1C

Evaluation of platelet function
We suggest preoperative platelet function testing only in addition to a positive bleeding anamnesis. 2C

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions and antiplatelet medication. 2C

Preoperative correction of anaemia
We recommend that patients at risk of bleeding are assessed for anaemia 4–8 weeks before surgery. 1C

If anaemia is present, we recommend identifying the cause (iron deficiency, renal deficiency or inflammation). 1C

We recommend treating iron deficiency with iron supplementation (oral or intravenous). 1B

If iron deficiency has been ruled out, we suggest treating anaemic patients with erythropoietin-stimulating agents. 2A

If autologous blood donation is performed, we suggest treatment with erythropoietin-stimulating agents in order to avoid preoperative anaemia and increased overall transfusion rates. 2B

Optimising macrocirculation
We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient. 1B

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Table 1 Grades of recommendation – GRADE system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation. High quality evidence.</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa.</td>
<td>Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation. Moderate quality evidence.</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa.</td>
<td>Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and may change the estimate.</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation. Low quality evidence.</td>
<td>Benefits appear to outweigh risk and burdens, or vice versa.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation. High quality evidence.</td>
<td>Benefits closely balanced with risks and burdens.</td>
<td>Consistent evidence from well performed, randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation. Moderate quality evidence.</td>
<td>Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens.</td>
<td>Evidence from randomised, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation. Low quality evidence.</td>
<td>Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.</td>
</tr>
</tbody>
</table>
We recommend the avoidance of hypervolaemia with crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac preload. 1B

We recommend against the use of central venous pressure and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimise preload during severe bleeding; dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead. 1B

We suggest the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol-based manner. 2C

Compared with crystalloids, haemodynamic stabilisation with iso-oncotic colloids, such as human albumin and hydroxyethyl starch, causes less tissue oedema. C

We suggest the use of balanced solutions for crystalloids and as a basic solute for iso-oncotic preparations. 2C

Transfusion triggers
We recommend a target haemoglobin concentration of 7–9 g dl\(^{-1}\) during active bleeding. 1C

Oxygen fraction
We recommend that inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding extensive hyperoxia (\(\text{PaO}_2 \geq 26.7\ \text{kPa} \ [200\ \text{mmHg}]\)). 1C

Monitoring tissue perfusion
We recommend repeated measurements of a combination of haematocrit/haemoglobin, serum lactate, and base deficit in order to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. These parameters can be extended by measurement of cardiac output, dynamic parameters of volume status (e.g. stroke volume variation, pulse pressure variation) and central venous oxygen saturation. 1C

Transfusion of labile blood products
We recommend that all countries implement national haemovigilance quality systems. 1C

We recommend a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products. 1A

We recommend photochemical pathogen inactivation with amotosalen and UVA light for platelets. 1C

We recommend that labile blood components used for transfusion are leukodepleted. 1B

We recommend that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions. 1C

We recommend that multiparous women be excluded from donating blood for the preparation of FFP and for the suspension of platelets in order to reduce the incidence of transfusion-related acute lung injury. 1C

We recommend that all RBC, platelet and granulocyte donations from first- or second-degree relatives be irradiated even if the recipient is immunocompetent, and all RBC, platelet and that granulocyte products be irradiated before transfusing to at-risk patients. 1C

We recommend the transfusion of leukocyte-reduced RBC components for cardiac surgery patients. 1A

Cell salvage
We recommend the routine use of red cell salvage which is helpful for blood conservation in cardiac operations using CPB. 1A

We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using CPB. 1A

We recommend the use of red cell salvage in major orthopaedic surgery because it is useful in reducing exposure to allogeneic red blood cell transfusion. 1A

We recommend that intraoperative cell salvage is not contraindicated in bowel surgery, provided that initial evacuation of soiled abdominal contents and additional cell washing are performed, and that broad-spectrum antibiotics are used. 1C

Storage lesions
We recommend that RBCs up to 42 days old should be transfused according to the first-in first-out method in, the blood services to minimise wastage of erythrocytes. 1C

Coagulation management
We recommend treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function. 1C

We recommend that a plasma fibrinogen concentration <1.5–2.0 g l\(^{-1}\) or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution. 1C

We suggest an initial fibrinogen concentrate dose of 25–50 mg kg\(^{-1}\). 2C

We suggest that the indication for cryoprecipitate is lack of available fibrinogen concentrate for the treatment of bleeding and hypofibrinogenaemia. 2C

In cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentrations, it is likely that FXIII activity is critically reduced. In cases of significant FXIII deficiency (i.e. <60% activity), we suggest that FXIII concentrate (30 IU kg\(^{-1}\)) can be administered. 2C

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We recommend that patients on oral anticoagulant therapy should be given prothrombin complex concentrate (PCC) and vitamin K before any other coagulation management steps for severe perioperative bleeding. 1B

We suggest that PCC (20–30 IU kg⁻¹) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients. 2C

We suggest that off-label administration of recombinant activated factor VII (rFVIIa) can be considered for bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. 2C

Antifibrinolytics and tranexamic acid
We recommend the consideration of tranexamic acid (20–25 mg kg⁻¹). 1A

We suggest the use of DDAVP under specific conditions (acquired von Willebrand syndrome). There is no convincing evidence that DDAVP minimises perioperative bleeding or perioperative allogeneic blood transfusion in patients without a congenital bleeding disorder. 2B

Correction of confounding factors
We recommend maintaining perioperative normothermia because it reduces blood loss and transfusion requirements. 1B

We suggest that rFVIIa may be used in treatment of patients with hypothermic coagulopathy. 2C

While pH correction alone cannot immediately correct acidosis-induced coagulopathy, we recommend that pH correction should be pursued during treatment of acidotic coagulopathy. 1C

We recommend that rFVIIa should only be considered alongside pH correction. 1C

We suggest that calcium should be administered during massive transfusion if Ca²⁺ concentration is low, in order to preserve normocalcaemia (≥0.9 mmol l⁻¹). 2B

Emergency radiological/surgical interventions to reduce blood loss
We suggest that endovascular embolisation is a safe alternative to open surgical intervention after failed endoscopic treatment for upper gastrointestinal bleeding. 2C

We suggest super-selective embolisation as primary therapy for treatment of angiogram positive lower gastrointestinal bleeding. 2C

We suggest embolisation as first-line therapy for arterial complications in pancreatitis. 2C

Cost implications
Bleeding and transfusion of allogeneic blood products independently increase morbidity, mortality, length of stay in ICU and hospital, and costs. B

Lysine analogues (tranexamic acid and e-aminocaproic acid; EACA) reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several settings of major surgery and trauma. A

We recommend restricting the use of rFVIIa to its licensed indication because, outside these indications, the effectiveness of rFVIIa to reduce transfusion requirements and mortality remains unproven and the risk of arterial thromboembolic events as well as costs are high. 1A

Cell salvage can be cost-effective. A

The cost-effectiveness of a formula-driven transfusion protocol has not been investigated.

Implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. B

Goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. B

Thromboembolic events are associated with increased in-hospital and post-hospital costs. B

Targeted therapy with fibrinogen and/or PCC guided by ROTEM/TEG is not associated with an increased incidence of thromboembolic events. C

Algorithms in specific clinical fields
Cardiovascular surgery
Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. A

Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of clopidogrel therapy increases the risk of bleeding. A

We recommend that a prophylactic dose of low molecular weight heparin should be administered subcutaneously 8–12 h before elective CABG surgery. This intervention does not increase the risk of perioperative bleeding. 1B

We recommend that tranexamic acid or EACA should be considered before CABG surgery. 1A

We suggest considering prophylactic preoperative infusion of 2 g fibrinogen concentrate in patients with fibrinogen concentration <3.8 g/L, because it may reduce bleeding following elective CABG surgery. 2C
Prothrombin complex concentrate is effective for rapid reversal of oral anticoagulation before cardiac surgery. A

We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high-, medium- and low-risk cardiovascular surgery. 1A

We recommend that tranexamic acid should be applied topically to the chest cavity to reduce postoperative blood loss following CABG surgery. 1C

We recommend that fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiovascular surgery. 1B

We suggest that recombinant FVIIa may be considered for patients with intractable bleeding during cardiovascular surgery once conventional haemostatic options have been exhausted. 2B

We suggest using preoperative intravenous iron to correct preoperative anaemia in women with menorrhagia. 2B

We recommend the use of standardised haemostatic algorithms with predefined intervention triggers. 1A

**Gynaecological (non-pregnant) bleeding**

We suggest against normovolaemic haemodilution because it does not reduce allogeneic transfusion. 2A

Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. C

We suggest using preoperative intravenous iron to reduce allogeneic transfusion requirements in gynaecological cancer patients receiving chemotherapy. 2B

We suggest using intravenous iron to correct preoperative anaemia in women with menorrhagia. 2B

Preoperative fibrinogen and D-dimer evaluation in gynaecological cancer patients provide little useful information. C

Postoperative FFP transfusion is associated with an increased risk of venous thromboembolism in malignant gynaecological surgery. C

rFVIIa increases thromboembolic risk and has not been shown to reduce mortality. B

Tranexamic acid reduces the frequency of late bleeding after cone biopsy of the cervix. B

Tranexamic acid reduces perioperative bleeding in gynaecological cancer surgery. C

We suggest against the use of tranexamic acid in benign gynaecological operations such as myomectomy. 2B

**Obstetric bleeding**

We recommend that peripartum haemorrhage should be managed by a multidisciplinary team. An escalating management protocol including uterotonics drugs, surgical and/or endovascular interventions, and procoagulant drugs should be available. 1C

Risk awareness and early recognition of severe haemorrhage are essential. C

We suggest that patients with known placenta accreta are treated by multidisciplinary care teams. 2C

Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation. C

We suggest that using perioperative cell salvage during caesarean section may decrease postoperative homologous transfusion and reduce hospital stay. 2B

We recommend that moderate (<9.5 g.dl$^{-1}$) to severe (<8.5 g.dl$^{-1}$) postpartum anaemia be treated with intravenous iron rather than oral therapy. 1B

Intravenous iron supplementation improves fatigue at 4, 8 and 12 weeks postpartum. B

Insufficient evidence exists to support the transfusion-sparing effect of intravenous iron supplementation.

We suggest that treatment with erythropoietin may correct anaemia more rapidly than treatment with folic acid and iron. 2C

We suggest assessing fibrinogen concentration in parturients with bleeding, as concentrations <2 g.l$^{-1}$ may identify those at risk of severe PPH. 2C

Platelet count $<100 \times 10^{9}$l$^{-1}$ at the onset of labour, particularly combined with plasma fibrinogen concentration $<2.9$ g.l$^{-1}$, may indicate an increased risk of PPH. C

aPTT and PT are of little predictive value for PPH. C

Thromboelastometry can identify obstetric coagulopathy and hyperfibrinolysis and guide haemostatic therapy. C

In life-threatening PPH, we suggest a transfusion protocol with a fixed product ratio or individualised procoagulant intervention and factor substitution. 2C

Considering physiologically elevated fibrinogen concentrations in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenaemia may be required. C
We recommend the administration of tranexamic acid in obstetric bleeding to reduce blood loss, bleeding duration and the number of units transfused. 1B

We suggest that tranexamic acid be considered before caesarean section. 2C

In antepartum bleeding, we suggest administration of tranexamic acid. 2B

We recommend that rFVIIa should only be considered as last line therapy because of its thromboembolic risk. 1B

We suggest that fibrinogen concentration and number of platelets should be optimised before administration of rFVIIa. 2C

Orthopaedic surgery and neurosurgery

In elective orthopaedic surgery, we recommend the implementation of a blood transfusion protocol (algorithm), together with staff education. 1B

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections. B

Infusion of colloids in patients with severe bleeding can aggravate dilutional coagulopathy by additional effects on fibrin polymerisation and platelet aggregation. C

We recommend that, for orthopaedic surgery, monotherapy with aspirin does not need to be discontinued. 1B

We recommend discontinuing dual antiplatelet therapy before urgent intracranial neurosurgery. A risk-benefit analysis is required for the continuation of aspirin monotherapy during neurosurgery. 1B

We recommend against performing orthopaedic surgery during the first three months after bare metal stent implantation or during the first twelve months after drug eluting stent implantation. 1C

Preoperative medication with ADP-receptor antagonists or with new oral anticoagulants is associated with an increased risk of major bleeding and intracerebral haemorrhage (ICH), especially if used in combination. B

Reduced platelet activity is associated with early haematoma growth, more intraventricular haemorrhage and worse three-month outcome following ICH. C

Low platelet count, low plasma fibrinogen concentration and FXIII deficiency are predictive of bleeding complications in ICH, intracranial surgery and major spine surgery, particularly when they occur in combination. C

Preoperative measurement of plasma fibrinogen concentration provides more information on bleeding volume and transfusion requirements than standard screening tests. C

We suggest the use of viscoelastic tests (ROTEM/TEG) for monitoring perioperative haemostasis in major orthopaedic surgery and neurosurgery. 2C

The intensity of oral anticoagulation with warfarin measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular with ICH. C

We suggest administering tranexamic acid in total hip arthroplasty, total knee arthroplasty, and major spine surgery. 2A

Tranexamic acid may promote a hypercoagulable state for some patients (with pre-existing thromboembolic events, hip fracture surgery, cancer surgery, age over 60 years, women). Therefore, we suggest an individual risk-benefit analysis instead of its routine use in these clinical settings. 2A

We suggest the use of rFVIIa in patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery. 2C

Prophylactic use of rFVIIa does not reduce perioperative blood loss or transfusion in non-haemophilic and non-coagulopathic patients undergoing major orthopaedic surgery or neurosurgery, and it may increase the incidence of thromboembolic events. We, therefore, recommend against the prophylactic use of rFVIIa in these clinical settings. 1B

We recommend restricting off-label use of rFVIIa to patients with severe bleeding who are unresponsive to other haemostatic interventions. 1C

In patients with INR > 1.5, with life-threatening bleeding or ICH, we recommend that four-factor PCCs (20–40 IU kg\(^{-1}\)), supplemented with vitamin K (10 mg by slow intravenous infusion), should be used for rapid reversal of vitamin K-antagonists (VKA). 1C

In patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery, we suggest using activated PCCs (e.g. FEIBA, FVIII inhibitor bypassing agents). 2C

New oral anticoagulants, such as rivaroxaban and dabigatran, may increase surgical bleeding and ICH growth. We suggest that PCC, FEIBA or rFVIIa may be used as non-specific antagonists in life threatening bleeding or ICH. 2C

Visceral and transplant surgery

Despite PT, aPTT and INR indicating coagulopathy in chronic liver disease (CLD), global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable CLD. C

Mild to moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. C

We recommend against the use of FFP for pre-procedural correction of mild to moderately elevated INR. 1C
We suggest a platelet count of $\leq 50 000 \, \mu l^{-1}$ as a threshold for platelet transfusion before liver biopsy. 2C

PFA-100 is not predictive of bleeding risk in cirrhosis. C

Bleeding time is influenced by many variables and is not useful to stratify bleeding risk. C

We recommend that, in acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion. 1C

Fluid restriction, phlebotomy, vasopressors and transfusion protocols may be associated with low transfusion rates during orthotopic liver transplantation (OLT). C

We recommend the use of perioperative coagulation monitoring using ROTEM/TEG for targeted management of coagulopathy. 1C

Antifibrinolytic therapy reduces blood loss and transfusion requirements in liver transplantation. B

We recommend antifibrinolytic drugs for treatment of fibrinolysis (evident from microvascular oozing or TEG/ROTEM clot lysis measurement) and not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis post-reperfusion. 1C

We recommend against rFVIIa for prophylaxis; rFVIIa should be used only as rescue therapy for uncontrolled bleeding. 1A

Point of care platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs. C

A low central venous pressure and restrictive fluid administration reduce bleeding during liver resection. B

We suggest that antifibrinolytic drugs should be considered in cirrhotic patients undergoing liver resection. 2C

**Acute upper gastrointestinal bleeding**

We recommend that acute variceal bleeding should be managed by a multidisciplinary team. A specific multimodal protocol for upper gastrointestinal haemorrhage should be available. 1C

We recommend that early treatment involves immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding and early interventional endoscopy. Antibiotics must be started on admission. 1A

Tranexamic acid reduces mortality but not rebleeding. B

rFVIIa should be used only as rescue therapy; we recommend against its routine use. 1C

**Coagulopathy and renal disease**

Point-of-care tests of platelet function and bleeding time provide no reliable platelet function assessment in uraemia and no prediction of bleeding in this setting. C

We suggest that conjugated oestrogen therapy should be used in uraemia. 2C

We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. 2C

There is no evidence to support use of rFVIIa in this setting.

**Paediatric surgery**

We suggest the use of perioperative coagulation analysis using viscoelastic point-of-care monitoring (ROTEM/TEG) for timely detection of coagulation defects including dilutional coagulopathy and hyperfibrinolysis. 2C

No clear recommendation can be made regarding the choice of perioperative fluid replacement in children. C

We suggest that a critical haemoglobin threshold of $8 \, g \, dl^{-1}$ for RBC transfusion may be safe in severe paediatric perioperative bleeding. 2C

We suggest that transfusion of platelet concentrates may be considered if platelet count is $<50 000–100 000 \, \mu l^{-1}$. 2C

No clear recommendation can be made regarding the indication and dosing of FFP transfusion in bleeding children, but severe side-effects have been reported. C

We suggest that fibrinogen concentrate (30–50 mg kg$^{-1}$) or cryoprecipitate (5 ml kg$^{-1}$) may be used to increase plasma fibrinogen concentrations above trigger values of 1.5–2.0 g l$^{-1}$ or FIBTEM MCF $>7$ mm in bleeding children. 2C

We suggest that FFP may be used if no other fibrinogen source is available. 2C

Data for PCC in children are limited and no dose recommendation can be made. C

No recommendation on the use of FXIII concentrate in bleeding children can be made.

We recommend against the use of rFVIIa in children. 1C

We suggest against the routine use of desmospressin in the absence of haemophilia A or mild von Willebrand disease. 2C

We suggest that perioperative antifibrinolytic therapy should be used to reduce blood loss and transfusion requirements in cardiac and non-cardiac paediatric surgery. 2A

**Antiplatelet agents**

We recommend that aspirin therapy should continue perioperatively in most surgical settings, especially cardiac surgery. 1C
Where aspirin withdrawal is considered, we recommend a time interval of 5 days. 1C

For intra- or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: \(0.7 \times 10^{11}\) [i.e. two standard concentrates] per 7 kg body weight in adults). 2C

Clopidogrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 5 days. 1C

Prasugrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 7 days. 1C

We recommend that antiplatelet agent therapy should resume as soon as possible postoperatively to prevent platelet activation. 1C

We suggest that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure. We also suggest that this first dose should not be a loading dose. 2C

We recommend postponement of elective surgery following coronary stenting (at least 6 to 12 weeks for bare metal stent and one year for drug-eluting stents). 1C

We recommend that a multidisciplinary team meeting should decide on the perioperative use of antiplatelet agents in urgent and semi-urgent surgery. 1C

We suggest that urgent or semi-urgent surgery should be performed under aspirin/clopidogrel or aspirin/prasugrel combination therapy if possible, or at least under aspirin alone. 2C

We suggest that platelet transfusion should be considered (dose: \(0.7 \times 10^{11}\) [i.e. two standard concentrates] per 7 kg body weight in adults) in cases of intra- or postoperative bleeding clearly related to clopidogrel or prasugrel. 2C

According to pharmacological characteristics, we suggest that the management of ticagrelor may be comparable to clopidogrel (i.e. withdrawal interval of 5 days). 2C

Platelet transfusion may be ineffective for treating bleeding clearly related to ticagrelor when given 12 h before. 2C

**Heparin**

We recommend that severe bleeding associated with intravenous unfractionated heparin (UFH) should be treated with intravenous protamine at a dose of 1 mg per 100 IU UFH given in the preceding 2–3 h. 1A

We suggest that severe bleeding associated with subcutaneous UFH unresponsive to intravenous protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of intravenous protamine, with dose guided by aPTT. 2C

We suggest that severe bleeding related to subcutaneous low molecular weight heparin (LMWH) should be treated with intravenous protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered. 2C

We suggest that severe bleeding associated with subcutaneous LMWH and unresponsive to initial administration of protamine could be treated with a second dose of protamine (0.5 mg per 100 anti-FXa units of LMWH administered). 2C

**Fondaparinux**

We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with subcutaneous administration of fondaparinux (off-label treatment). 2C

**Vitamin K antagonists**

We recommend that vitamin K antagonists (VKAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in VKA treated patients. 1C

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score \(\leq 2\), patients treated for > 3 months for a non-recurrent VTE) undergoing procedures requiring INR <1.5, VKA should be stopped 5 days before surgery. No bridging therapy is needed. Measure INR on the day before surgery and give 5 mg oral vitamin K if INR exceeds 1.5. 1C

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score > 2, patients with recurrent VTE treated for <3 months, patients with a mechanical valve). Day 5: last VKA dose; Day 4: no heparin; Days 3 and 2: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH twice or thrice daily; Day 1: hospitalisation and INR measurement; Day 0: surgery. 1C

We recommend that for groups 1 and 2 above, VKAs should be restarted during the evening after the procedure. Subcutaneous LMWH should be given postoperatively until the target INR is observed in two measurements. 1C

We recommend that for group 3 above, heparin (UFH or LMWH) should be resumed 6–48 h after the procedure. VKA can restart when surgical haemostasis is achieved. 1C

We recommend that, in VKA treated patients undergoing an emergency procedure or developing a bleeding complication, PCC (25 IU FIX kg\(^{-1}\)) should be given. 1B

We recommend to assess creatinine clearance in patients receiving NOAs and being scheduled for surgery. 1B
New oral anticoagulants
We suggest that new oral anticoagulant agents (NOAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery, (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in NOA treated patients. 2C

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score ≥2, patients treated for <3 months for a non-recurrent VTE) undergoing procedures requiring normal coagulation (normal diluted thrombin time or normal specific anti-FXa level), NOAs can be stopped 5 days before surgery. No bridging is needed. 1C

In patients treated with rivaroxaban, apixaban, edoxaban and in patients treated with dabigatran in which creatinine clearance is higher than 50 ml min⁻¹, we suggest bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score ≥2, patients with recurrent VTE treated for <3 months). Day 5: last NOA dose; Day 4: no heparin; Day 3: therapeutic dose of LMWH or UFH; Day 2: subcutaneous LMWH or UFH; Day 1: last injection of subcutaneous LMWH (in the morning, i.e. 24 h before the procedure) or subcutaneous UFH twice daily (i.e. last dose 12 h before the procedure), hospitalisation and measurement of diluted thrombin time or specific anti-FXa; Day 0: surgery. 2C

In patients treated with dabigatran with a creatinine clearance between 30 and 50 ml min⁻¹, we suggest to stop NOAs 5 days before surgery with no bridging. 2C

We suggest that for groups 2 and 3, heparin (UFH or LMWH) should be restarted 6–72 h after the procedure, taking the bleeding risk into account. NOAs may be resumed when surgical bleeding risk is under control. 2C

Patients with congenital bleeding disorders

Von Willebrand disease
We suggest that if VWD is suspected preoperatively, the patient be referred to a haematologist for assessment and planning of the intervention. 2C

We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding. 1C

We recommend that patients with VWD be managed perioperatively in collaboration with a haematologist. 1C

We recommend desmopressin as a first-line treatment for minor bleeding/surgery in patients with VWD, after a trial testing. The regimen is specified by published guidelines. 1C

We recommend replacement of VWF with plasma-derived products for major bleeding/surgery. Treatment regimens are specified by published guidelines. 1C

We suggest that antifibrinolytic drugs be used as haemostatic adjuncts. Treatment regimens are specified by published guidelines. 2C

We suggest that platelet transfusion may be used only in case of failure of other treatments. 2C

Platelet defects
We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited platelet defects are suspected preoperatively. 2C

We recommend the use of a bleeding assessment tool for predicting the perioperative risk of bleeding. 1C

We recommend that patients with severe inherited platelet disorders should be managed perioperatively in collaboration with a haematologist. 1C

We suggest preoperative haemostatic correction in patients with inherited platelet disorders. 2C

We suggest desmopressin be used to prevent/control perioperative bleeding in patients with inherited platelet defects. 2C

We suggest antifibrinolytic drugs be used as haemostatic adjuncts in procedures involving patients with inherited platelet defects. 2C

We recommend that rFVIIa treatment should be considered in patients with Glanzmann thrombasthenia undergoing surgery. 1C

We recommend against routine platelet transfusion in patients with inherited platelet disorders. 1C

There is insufficient evidence to recommend a threshold for perioperative prophylactic platelet transfusion in thrombocytopenic patients. C

Comorbidities involving haemostatic derangement

We suggest that patients with haemostatic derangements associated with systemic, metabolic and endocrine diseases should be managed perioperatively in collaboration with a haematologist. 2C

We suggest that selective serotonin reuptake inhibitor (SSRI) treatment should not be routinely discontinued perioperatively. 2B

We suggest individualised perioperative discontinuation of antiepileptic agents, such as valproic acid, which may increase bleeding. 2C

We do not recommend discontinuation of Gingko biloba extracts. 1B
Haemophilia A and B
We recommend that haemophilia patients should be referred preoperatively to a haematologist for assessment/intervention. 1C
We recommend that surgery in haemophilia patients should be performed in specialised centres with expertise in coagulation disorders. 1C
We recommend adequate perioperative replacement therapy to ensure safe surgery in haemophilia patients. 1C
We suggest that perioperative replacement therapy (target factor level and duration) in haemophilia patients follows published guidelines. 2C
We recommend either recombinant products or plasma-derived concentrates for perioperative replacement therapy in haemophilia patients 1C
We suggest that coagulation factors be given perioperatively by continuous infusion. 2C
We suggest either rFVIIa or activated PCCs for haemophilia patients with inhibitors. 2C
We suggest antifibrinolytic drugs as perioperative adjunct therapy in haemophilia patients. 2C
We suggest individualised perioperative thromboprophylaxis in haemophilia patients. 2C

Rare bleeding disorders
We recommend that patients with rare bleeding disorders should be referred preoperatively to a haematologist for assessment/intervention. 1C
We recommend that surgery in patients with rare bleeding disorders should be carried out in consultation with a haematologist with experience in factor deficiencies. 1C
There is insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders. C
We suggest that rFVIIa be used in perioperative bleeding due to inherited FVII deficiency. 2C
If rFVIIa is given to control perioperative bleeding in inherited FVII deficiency, we suggest lower doses than in haemophilia patients. 2C
There is insufficient data to recommend rFVIIa in perioperative bleeding for patients with other rare bleeding disorders. C
There is insufficient data to recommend peri-procedural desmopressin or antifibrinolytic drugs in patients with mild rare bleeding disorders. C
3 INTRODUCTION
Healthcare professionals face an increasingly difficult task in keeping up to date with the evidence on perioperative transfusion strategies, as the number of studies published in this area has increased dramatically during the last 20 years. Within the last 10 years alone, more than 100 different medical journals have published relevant systematic reviews. This not only reflects the complexities of transfusion medicine but also the development of alternatives to transfusion and the move towards evidence-based perioperative practice. Thus, it is imperative to update evidence-based transfusion guidelines for healthcare professionals and researchers.

Particularly urgent is the need to assess the mounting evidence in support of restrictive transfusion strategies as being not only safe but also potentially beneficial in terms of mortality, morbidity, postoperative outcomes and long-term survival in both cardiac and non-cardiac surgery patients. This evidence is challenged by the widespread practice of perioperative allogeneic blood transfusion, especially in cardiac surgery, where 40–90% of patients receive blood transfusions, using approximately 10–15% of the national supply of blood. There is also an urgent need to consider potential resource utilisation issues associated with aggressive use of blood products, as their preparation and storage are expensive. Growing evidence indicates that measures to support and monitor coagulation, such as antifibrinolytic drugs, point-of-care technologies (e.g. thrombelastography, thromboelastometry) and fluid therapy, are important for quality improvement and may offer alternative effective approaches for limiting blood transfusion and decreasing perioperative bleeding. However, as many of the current indications for, and alternatives to, transfusion are not based on high quality evidence, there is a need for well designed and performed clinical trials, and high quality systematic reviews. Many of the existing data are from retrospective studies (with their inherent shortcomings) and more randomised clinical trials are urgently needed.

This guideline by the European Society of Anaesthesiology (ESA) aims to provide an up-to-date review and synthesis of the evidence, with recommendations which may guide practitioners towards safe and cost-effective strategies for minimising severe non-traumatic perioperative bleeding and maximising blood conservation. Additionally, this guideline will identify knowledge gaps and new clinical questions which will guide the design of future clinical trials. Acknowledging the variation in transfusion practices across countries, hospitals, specialties and surgical procedures, concerted efforts will be needed for rapid implementation of this guideline, promotion of safe and appropriate transfusion, avoidance of unnecessary transfusion, discontinuation of potentially harmful practices and assessment of novel strategies.

4 METHODS
4.1 Selection of task force
In June 2010, the ESA Guideline Committee, chaired by Andrew Smith, nominated the chairperson of the Subcommittee on Transfusion and Haemostasis, Sibylle Kozek-Langenecker, to coordinate the core group of the task force, consisting of the Subcommittee chairpersons Patrick Wouters (circulation), Cesar Santullano (intensive care medicine) and Eduardo de Robertis (resuscitation and emergency medicine), and Subcommittee members Arash Afshari (evidence based practice) and Klaus Görlinger (transfusion and haemostasis). The ESA Guideline Committee defined the broad scope of the guideline project, which prompted the core group to invite 15 anaesthetist experts into the task force as affiliate co-authors. Georgina Imberger (Copenhagen Trial Unit and Cochrane Anaesthesia Review Group) was invited into the task force for the evidence search.

4.2 The search for evidence
To develop the scope of the guidelines, the task force defined a series of key clinical questions about the management of severe perioperative bleeding, a process completed in October 2010. These questions formed the basis for reviewing the evidence and developing the recommendations.

We used three approaches to search for relevant published evidence. First, we conducted a broad search on MEDLINE and Embase using exploded terms for ‘anaesthesia’ and ‘surgery’, combined with ‘bleeding’ or ‘blood loss’ in the title. This search was conducted in December 2010 and included all publications from the previous 10 years. The exact search strategy is detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). A total of 9376 citations were retrieved and reviewed for possible inclusion.

Second, we conducted more specific MEDLINE and Embase searches when necessary in some areas. Search terms were developed with the help of the task force members responsible for the given section. The exact searches are detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). The searches were conducted between January and May 2011, and included all publications from the previous 10 years. A total of 20 664 citations were retrieved and reviewed for possible inclusion. The search was repeated for the last sections to be included (6.3, 5.1) between May 2011 and May 2012. Third, we conducted a broad search for systematic reviews of anaesthesiological interventions. The exact search strategy is detailed in the Appendix (Supplemental Digital Content, http://links.lww.com/EJA/A31). We searched MEDLINE and Embase, with no time restrictions. A total of 11 869
citations were retrieved and reviewed for possible inclusion.

From these three approaches, a total of 2686 publications were selected for possible inclusion. We included systematic reviews, randomised controlled trials, cohort studies, case control studies and cross-sectional surveys. We did not include existing guidelines, narrative reviews, editorials, case series or case reports. We did not use language restrictions.

Task force members reviewed the selected articles relevant to their sections. Our goal was to include all relevant and robust evidence in these guidelines. Therefore, we included evidence that was sourced separately from the approaches described above and considered references cited in published trials, sometimes leading to the inclusion of trials published more than 10 years ago. Other evidence was sourced from the personal clinical and academic experience of the task force members.

The expertise of the task force guided the selection of trials for inclusion, thereby involving a subjective assessment of a study’s relevance. Once selected, we reviewed trials for their quality and applicability. According to the suggestion of the ESA Guideline Committee, we used the Scottish Intercollegiate Guidelines Network (SIGN) grading system to assess the level of evidence of a study and to grade our recommendations based on the body of supporting evidence. During the process of guideline development, the official position of the ESA changed, matching many other scientific organisations in favouring the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Therefore, all of our recommendations and suggestions are assigned a number (relating to the strength of the recommendation) and a letter (relating to the quality of the supporting evidence) according to the GRADE system (Table 1). Statements are accompanied only by a letter. According to the broad scope of the guideline project, the initial manuscript was approximately 98 000 words in length. In order to increase readability and future implementation, by May 2012 the contents of all sections had been condensed by approximately 46% and a list of recommendations was prepared (Section 2. Summary).

4.3 Review of the guideline

These guidelines have undergone the following review process. The final draft was reviewed by members of the relevant Subcommittees of the ESA’s Scientific Committee who were not involved in the initial preparation of the guideline, as well as by external reviewers. The draft was posted on the ESA website from 13 July 2012 to 19 August 2012 and all ESA members, individual and national, were contacted by electronic mail to invite them to comment. Comments were collated by the chair of the guideline task force and the guideline was amended as appropriate. The final manuscript was approved by the Guidelines Committee and Board of the ESA before submission for publication in the European Journal of Anaesthesiology. Because of the increasing evidence in this field, an update of the guidelines is planned every two years.

5 COAGULATION MONITORING

5.1 Perioperative coagulation testing

5.1.1 Introduction

Traditionally, perioperative coagulation monitoring has relied on clinical judgement and standard laboratory tests (SLTs). However, many SLTs were designed to test for coagulation factor deficiencies, not for predicting risk of bleeding or guiding haemostatic management. Moreover, utility of SLTs in emergency situations is limited by slow turnaround times due to sample transport and plasma preparation requirements. In contrast, viscoelastic point-of-care monitoring enables rapid intraoperative diagnosis of the cause of bleeding. This section examines assays used to diagnose coagulation status perioperatively.

5.1.2 Standard laboratory tests for coagulation monitoring

SLTs can be performed using automated analysis, with instrumentation, reagents and detection methods varying between institutions. However, the principles underlying individual SLTs are consistent across platforms.

5.1.2.1 Activated partial thromboplastin time

Activated partial thromboplastin time (aPTT) measures overall integrity of the intrinsic and common coagulation pathways. Recalified, citrated plasma is incubated at 37°C with partial thromboplastin and an activator. Clotting time (time to fibrin strand formation) is recorded. aPTT is affected by levels of fibrinogen and coagulation factors II, V, VIII, IX, XI, and XII, and is influenced by temperature, pH, heparin and oral anticoagulants. aPTT indicates multiple coagulation factor deficiencies more clearly than it does single factor deficiencies.

5.1.2.2 Prothrombin time

Prothrombin time (PT) measures integrity of the extrinsic and common pathways; it is affected by levels of fibrinogen and coagulation factors II, V, VII and X. Recalified, citrated plasma and tissue thromboplastin are incubated at 37°C. Clotting time is recorded as for aPTT. PT measurements can be standardised by conversion to an international normalised ratio (INR) to allow monitoring of anticoagulant therapy with coumarins.

5.1.2.3 Fibrinogen concentration

Fibrinogen is essential for effective coagulation and is the first factor to be depleted during massive bleeding and haemodilution. Its concentration is often determined...
indirectly using the Clauss method. Diluted, citrated plasma is activated with thrombin, and clotting time is recorded as for PT and aPTT. Fibrinogen concentration is inversely proportional to clotting time, and is calculated using calibration standards. Clauss assays are sensitive to heparin, fibrinogen degradation products and colloids such as hydroxyethyl starch. Fibrinogen levels can also be determined using a PT-based assay, although this may be too variable for clinical use. Alternatively, immunological detection is possible using antifibrinogen antibodies, providing a measure of fibrinogen quantity but not functionality.

5.1.2.4 Platelet count
In the perioperative setting, platelet count (concentration) is commonly measured. This, however, does not assess the functional activity of platelets.

5.1.2.5 Assaying specific coagulation factors
Tests for individual coagulation factors, including factors II, V, VII, VIII, IX, X and XIII, can be used to confirm specific deficiencies (e.g. congenital). Other biomarkers of coagulation and fibrinolysis can also be measured, such as D-dimers for exclusion of pulmonary embolism and deep vein thrombosis.

5.1.3 Point-of-care coagulation monitoring
Point-of-care (POC) coagulation monitoring uses whole blood and is performed in the emergency room, operating theatre, or the central laboratory. Turnaround times for POC tests are shorter than for SLTs. As with SLTs, POC coagulation monitoring can be performed using various analytical platforms and reagents, so this section will focus on assay principles. For global coagulation analysis, the principal POC tests use thrombelastography (TEG; Haemoscope Inc., Niles, IL) or thromboelastometry (ROTEM; Tem International GmbH, Munich, Germany), which each operate on similar principles. Unless stated otherwise, the term ‘POC coagulation monitoring’ within this section refers to TEG/ROTEM assays.

5.1.3.1 Parameters recorded using point-of-care coagulation monitoring
Blood samples for POC coagulation analysis are placed in a reaction chamber and a pin is immersed. Oscillation is introduced and viscoelasticity of the sample is measured via movement of the pin. As the blood clots, fibrin polymerisation progressively changes the viscoelasticity. Overall, POC coagulation assays are more representative of in vivo coagulation than conventional laboratory tests.

Unlike SLTs, POC coagulation monitoring extends beyond initial fibrin polymerisation. The clot formation and degradation profile can be assessed for up to 60 min, with coagulation dynamics represented graphically. Numerical values indicate the speed and quality of clot formation.

Coagulation initiation. Recorded as reaction (t) time or clotting time (CT), both parameters represent the time to reach an amplitude of 2 mm (i.e. initiation of clot formation, partially dependent on thrombin generation).

Clot formation. Time for amplitude to increase from 2 to 20 mm, expressed as k time or clot formation time (CFT). The alpha (α) angle (tangent of the slope between 2 and 20 mm) provides another measure of clot formation rate.

Clot strength. Maximum amplitude (MA) or maximum clot firmness (MCF), both measured in mm, represent the combined effects of platelet aggregation and fibrin polymerisation. Clot rigidity (G) and maximum clot elasticity (MCE) may also be used to assess clot strength. G and MCF have a curvilinear relationship with MA and MCF, respectively, making them conceptually and statistically important. Amplitude at early time-points (A5, A10, etc.) may be used to predict maximum clot firmness.

Clot stability. This is measured by reduction of clot strength after MA or MCF has been reached, and typically expressed as lysis index (LY30 or LI30; % of clot strength remaining 30 min after MA or CT, respectively). Maximum lysis (ML; greatest % decrease in amplitude from MCF observed during the assay period) is also used. Low lysis index or high ML can indicate hyperfibrinolysis.

5.1.3.2 Commonly used blood modification agents for POC coagulation assays
POC coagulation monitoring can be performed using recalculated, citrated blood alone (NATEM assay; clotting initiated intrinsically by the surface of the cup and pin). More usually, activators are added to accelerate coagulation, and modifying agents can suggest the cause of observed coagulopathy. The following are the most commonly used assays.

Intrinsic activation (e.g. kaoTEG or INTEM assay). Addition of a contact activator (e.g. kaolin or ellagic acid) stimulates intrinsic activation, providing an assay analogous to aPTT.

Extrinsic activation (e.g. rapidTEG or EXTEM assay). Addition of (recombinant) tissue factor (TF) activates coagulation via the extrinsic pathway, providing an assay analogous to PT.

Heparin anticoagulation (e.g. hepTEG or HEPTEM assay). Addition of heparinase to an intrinsically activated assay degrades heparin in the blood, enabling identification of coagulopathy caused by heparin.

Fibrin clot quality (e.g. functional fibrinogen [FF] or FIBTEM assay). This involves addition of a platelet inhibitor (e.g. abciximab or cytochalasin D) to an extrinsically activated assay. This test measures strength of the fibrin-based clot. Low FF/FIBTEM clot strength usually indicates fibrinogen deficiency. Adequate FF/FIBTEM
clot strength in the presence of decreased overall clot strength in bleeding patients may indicate platelet deficiency.

**Hyperfibrinolysis (e.g. APTEM assay).** This involves addition of the antifibrinolytic agent aprotinin to an extrinsic activation assay. Improved coagulation with aprotinin indicates hyperfibrinolysis.

POC devices with multiple channels allow several assays (e.g. extrinsic, intrinsic, fibrinogen and hyperfibrinolysis) to be performed simultaneously.

**5.1.4 Which approaches can be used for preoperative evaluation of coagulation status?**

Preoperative coagulation monitoring may influence subsequent decisions concerning the management of perioperative bleeding. Bleeding risk may be elevated by congenital coagulation disorders such as von Willebrand disease (VWD) or by routine medication for underlying conditions. Coagulation tests may suggest increased bleeding risk, but they cannot predict intraoperative or postoperative bleeding caused by exogenous factors. Thoracic or abdominal procedures lasting >2 h and with blood loss >500 ml carry particular risks, and may require laboratory analysis for bleeding risk stratification.45

**5.1.4.1 Standardised bleeding history and clinical evaluation**

**Recommendation**

*We recommend the use of a structured patient interview or questionnaire before surgery or invasive procedures, which considers clinical and family bleeding history and detailed information on the patient’s medication.1C*

Structured patient interviews are a primary tool for preoperative assessment of bleeding risk. Clinical and family history and current drug therapy are considered. Recent guidelines from the UK, Austria and Italy recommend structured questionnaires.34,45–47 Investigations have shown that such questionnaires identify patients at risk of bleeding.48–53 In a study by Eberl et al.,49 a positive predictive value of 9.2% was reported for the use of standardised bleeding history. In addition, three groups have strongly recommended a questionnaire instead of SLTs.48,51,57 Data suggest that these questionnaires also have the potential to quantify the risk of bleeding for inherited coagulopathies.58

Physical examination should be performed as a second step, focusing on signs of bleeding and diseases which may cause haemostatic failure (e.g. liver disease, inherited coagulation abnormalities).59 Physical examination can detect bleeding disorders not identified by conventional tests (e.g. scurvy presenting with soft tissue bleeding).53 Gender, body mass index and comorbidities including arterial hypertension, diabetes mellitus and renal dysfunction are independent risk factors for bleeding and transfusion.60–68

**5.1.4.2 Preoperative use of standard laboratory tests**

Application of preoperative SLTs is well covered by existing guidelines.34,46,80 However, current ESA guidelines do not recommend their use.81 SLTs were originally designed to indicate coagulation factor deficiencies, not to assess clinical risk of haemorrhage.82,83 Normal ranges for PT and aPTT are based on the general population and may not apply to surgical patients with massive bleeding.82 Accordingly, aPTT and PT fail to identify occult bleeding disorders among paediatric patients at high risk of bleeding.84

Low preoperative fibrinogen concentrations potentially indicate increased risk of intraoperative bleeding during cardiac surgery.85,86 In the obstetric setting, fibrinogen measurement is reported as the parameter best correlated with postpartum bleeding volume and haemostatic impairment.87 Preoperative measurement of fibrin monomer or fibrin degradation product may also allow risk stratification for intraoperative blood loss.88,89

SLTs are typically performed using plasma, with platelets and other blood cells removed, and thus do not reflect the true physiological clotting process.90 Nor can SLTs provide rapid assessment of fibrinolysis, platelet dysfunction, or haemostatic response to injury or surgery. A systematic review found that abnormal SLT results do not predict intra- or postoperative bleeding.91 False positive and false negative results are likely,92 necessitating further tests and incurring additional costs. Italian
guidelines recommend routine preoperative PT, aPTT and platelet count assessment. However, in patients without a previous history of bleeding or bleeding disorders, SLTs are not generally recommended. Selective laboratory testing is advised because it is more cost-effective and more evidence based. Preoperative assessment of aPTT, PT, INR, fibrinogen and platelet count is warranted in patients with bleeding disorders, a history of bleeding or a clear clinical indication (e.g. HELLP syndrome [haemolysis, elevated liver enzymes and low platelets], liver disease, leukaemia or haemophilia). There is currently little evidence to support additional, routine application of point-of-care INR testing in the preoperative setting to predict bleeding tendency, despite the fact that many recent devices provide results which are comparable with laboratory testing.

5.1.4.3 Preoperative use of POC coagulation monitoring
Preoperative POC measurement of coagulation does not predict bleeding during or after surgery. POCT monitoring assays are instead designed for rapid diagnosis of bleeding causes, which is of most value intraoperatively. Indiscriminate preoperative coagulation monitoring using POC assays is unlikely to be cost-effective, but it may be warranted in combination with SLTs in patients with bleeding disorders such as VWD, factor XII deficiency, and haemophilia A with dysfibrinogenemia.

5.1.4.4 What is the role of genetic predictors?
In neurosurgery patients, tumour necrosis factor-alpha polymorphism is associated with increased bleeding risk. Low levels of plasminogen activator inhibitor-1 (PAI-1) correlate with increased bleeding risk in transurethral resection of the prostate. PAI-1 polymorphism may also influence bleeding risk in cardiac surgery. Polymorphism of GPIIb/IIIa can exacerbate bleeding in cardiac surgery following aspirin pretreatment. Angiotensin converting enzyme II genotype may be associated with reduced blood loss in geriatric patients undergoing hip arthroplasty. In addition, polymorphisms have been identified in seven distinct factors which may contribute to the wide variation in bleeding tendency. E-selectin polymorphism has also been identified as a risk factor for increased bleeding during cardiopulmonary bypass (CPB).

Currently, no recommendation can be made on the value of genetic testing for evaluating bleeding risk.

5.1.4.5 What is the best approach for preoperative evaluation of coagulation status?
Assessment of bleeding history, including physical examination, remains the best tool for identifying patients with increased risk of perioperative bleeding complications. If bleeding history is positive, clinical signs of bleeding tendency are present, or if the planned operation requires special consideration, comprehensive assessment is indicated. Otherwise, the only crucial blood analysis is ABO blood grouping.

5.1.5 Which coagulation monitoring tests can be used to guide intraoperative haemostatic therapy?
Correct diagnosis of the cause of bleeding is essential for effective haemostatic intervention. In emergency situations and high-risk surgical procedures, this diagnosis must be made as quickly as possible. Intervention can be guided by clinical judgement, SLTs or POC monitoring. We discuss the evidence for each below.

5.1.5.1 Intraoperative use of standard laboratory tests
Several guidelines have explored intraoperative use of SLTs. There is little evidence to support their utility in this setting. Measurement of fibrinogen (Clauss method), D-dimer and antithrombin (AT) may, in conjunction with clinical assessment and SLTs, facilitate diagnosis or exclusion of disseminated intravascular coagulation (DIC). This approach, however, is incompatible with emergency situations because SLTs have typical turnaround times of 30–60 min. Accordingly, the applicability of SLTs in trauma has never been proven. In cardiovascular surgery, hypofibrinogenemia has been identified as a major factor contributing to haemorrhage after CPB; however, for laboratory measurement of fibrinogen to be useful, analysis would need to begin before the patient is removed from CPB, which is prevented by sensitivity of the Clauss assay to heparin. In liver transplantation, attempts to establish transfusion triggers for haemostasis management, based either on SLTs or POC monitoring assays, have been inconclusive.

There is insufficient data to recommend routine intraoperative coagulation monitoring using SLTs. Conversely, recent Italian guidelines recommend prolonged PT and aPTT (>1.5 times normal) as a trigger for administration of fresh frozen plasma (FFP); the same guidelines also suggest ‘blind’ FFP administration if the tests cannot be performed within a reasonable time. A recent review of haemostatic test results during postpartum haemorrhage found that FFP was routinely over administered with respect to guidelines for PT- and aPTT-guided transfusion. Moreover, fibrinogen concentrations declined in many patients despite excessive FFP transfusion, suggesting that alternative interventions may have been more suitable.

5.1.5.2 Intraoperative use of point-of-care coagulation monitoring
A recent Cochrane review showed a lack of evidence that POC monitoring improves mortality compared with ‘usual care’. This is unsurprising given that POC monitoring assays only establish the presence and cause
of haemostatic impairment; it is the subsequent interventions that influence patient outcome. Bleeding may be reduced by improving consistency of therapeutic decisions, using different transfusion triggers or using alternative interventions. For example, POC monitoring is used to guide administration of coagulation factor concentrates, which has been shown to decrease allogeneic blood product transfusion requirements and was associated with improved outcomes.\textsuperscript{116–120} The techniques (e.g. thrombelastography) and devices (e.g. TEG) are routinely given prominence over the individual assays. Some studies have used a single assay (e.g. kaolin activation)\textsuperscript{121,122} but simultaneous performance of several assays may be critical for accurate diagnosis of bleeding causes. Selection of appropriate assays for POC diagnosis should be considered carefully.\textsuperscript{123}

**Intraoperative point-of-care monitoring in trauma.** POC coagulation monitoring has been used in case studies and patient cohorts to diagnose and treat bleeding in trauma patients.\textsuperscript{119,124–126} CT and MCF from extrinsic activation (TF) and fibrin clot quality (TF + cytochalasin D) assays,\textsuperscript{118,124,125} as well as CT, CFT and MCF from intrinsic activation (ellagic acid) assays,\textsuperscript{126} have been used successfully to monitor haemostasis and guide treatment with fibrinogen concentrate and prothrombin complex concentrate (PCC). Such treatment has been shown to reduce exposure to allogeneic blood products compared with non-standardised strategies which do not utilise POC coagulation monitoring.\textsuperscript{118} The evidence suggests that POC assays measuring extrinsic activation and fibrin clot quality may be useful to guide administration of fibrinogen concentrate and PCC in trauma. Prospective, randomised trials are now required.

Additional case studies describe POC coagulation monitoring in trauma patients. Nylund \textit{et al.}\textsuperscript{127} reported rFVIIa administration in a paediatric trauma patient in response to poor k and a-angle values obtained by intrinsic (kaolin) activation assay. Walker \textit{et al.}\textsuperscript{128} reported the assessment of MCF in extrinsic (TF) and fibrin clot quality (TF + cytochalasin D) assays before epidural insertion after massive transfusion.

**Intraoperative point-of-care monitoring in cardiovascular surgery.** The value of POC monitoring to guide haemostatic therapy following CPB has been demonstrated in several randomised, controlled trials.\textsuperscript{119,121,129} In one of them, four parallel assays (intrinsic [ellagic acid], intrinsic + heparinase, extrinsic [TF] + aprotinin, and extrinsic + cytochalasin D) were used to guide haemostatic intervention in patients undergoing aortic surgery with circulatory arrest.\textsuperscript{129} Furthermore, first-line therapy with fibrinogen concentrate and PCC based on POC testing was associated with decreased transfusion requirements and a decreased incidence of thromboembolic events in a cohort study including 3865 patients\textsuperscript{120} as well as in a prospective randomised controlled trial including 100 patients.\textsuperscript{119} In this latter study, the use of an algorithm based on POC testing was associated with improved outcomes including significantly reduced mortality. Routine use of such algorithms could reduce transfusion requirements, improve outcomes and lower costs.

Prospective studies have also demonstrated the utility of MCF from fibrin clot quality assessment (TF + cytochalasin D) to guide administration of fibrinogen concentrate in cardiovascular surgery patients (target MCF: 22 mm).\textsuperscript{116,117} These studies suggest that individualised fibrinogen concentrate dosing, based on target MCF values, may decrease blood loss and transfusion requirements following CPB.

Similar individualised dosing of cryoprecipitate, based on A10 values from fibrin clot quality assays (TF + cytochalasin D), has been reported following elective CPB.\textsuperscript{131} Prediction of cryoprecipitate requirements using this approach has high sensitivity and specificity.

**Intraoperative point-of-care monitoring in liver surgery.** Individualised (‘theragnostic’) dosing of cryoprecipitate using thrombelastography has been described in a liver transplant patient with afibrinogenaemia.\textsuperscript{132} More recently, a transfusion algorithm based on POC intrinsic (kaolin) activation test results was compared with an SLT based protocol in orthotopic liver transplantation (OLT) patients.\textsuperscript{133} Mortality was unaffected and the authors reported reduced exposure to FFP using the POC guided algorithm. Overall, the results indicate that POC intrinsic activation assays can be used to guide transfusion during OLT surgery.

A retrospective study investigated routine POC monitoring of fibrinolysis in OLT, using extrinsic (TF) activation and hyperfibrinolysis (TF + aprotinin) tests to determine whether tranexamic acid should be administered.\textsuperscript{134} This targeted approach to antifibrinolytic therapy may improve patient responses and reduce exposure to FFP.

**Intraoperative point-of-care monitoring in obstetrics.** POC assays with intrinsic (ellagic acid) and extrinsic (TF) activation, as well as fibrin clot quality (TF + cytochalasin D), have been compared in pregnant women and non-pregnant controls.\textsuperscript{135} Clotting time and clot formation time were reduced and clot strength was increased in the pregnant group, demonstrating hypercoagulability. Studies are needed to ascertain the potential use of POC monitoring for treating postpartum bleeding, and to determine an appropriate range of reference values for these patients.

Additional POC techniques have been described, for example, POC assessment of PT and INR, which appears to be rapid and accurate.\textsuperscript{136} However, the usefulness of PT/INR may be limited outside the setting of vitamin K antagonist anticoagulation.
5.1.6 Postoperative evaluation of coagulation status

Potential complications following surgery include thromboembolic events and, conversely, recurrent or excessive bleeding. Postoperative coagulation monitoring in the intensive care unit (ICU) can provide information regarding appropriate haemostatic interventions or further procedures which may be required.

Kashuk et al.137 assessed the use of POC extrinsic (TF) activation tests to identify critically ill patients at risk of thromboembolic events. Hypercoagulability, defined as G >12 400 dyn cm⁻², was confirmed in 86/152 patients. Clot strength (MA from POC assays) has been used to measure the effects of clopidogrel after coronary artery bypass surgery.138 In splenectomised thalassaemic patients, whole blood intrinsic (ellagic acid) and extrinsic (TF) activation assays consistently indicated hypercoagulability, while thrombin generation tests performed using platelet-poor plasma did not.139 Other evidence from POC assays, aPTT, platelet counts and fibrinogen measurement has confirmed a tendency towards hypercoagulability following splenectomy.140 Current evidence suggests that POC measurements of the speed of clot initiation, formation and strength/elasticity/rigidity, can identify patients at risk of thromboembolic events.

There is minimal evidence to support using either SLTs or POC coagulation monitoring to guide haemostatic intervention in the postoperative period. Trials comparing POC guided transfusion with conventional coagulation management have included analysis of samples drawn up to 24 h after CPB, but have not reached specific conclusions on the importance of postoperative monitoring.121,129

5.1.7 Are patient outcomes improved by algorithms that incorporate coagulation monitoring for perioperative haemostatic management?

Recommendations

We recommend the application of transfusion algorithms incorporating predefined intervention triggers to guide haemostatic intervention during intraoperative bleeding. 1B

We recommend the application of transfusion algorithms incorporating predefined intervention triggers based on POC coagulation monitoring assays to guide haemostatic intervention during cardiovascular surgery. 1C

Haemostatic intervention in bleeding patients is generally determined empirically. Consequently, transfusion practices differ substantially among institutions.141–143 To reduce this variability, guidelines typically recommend administration of blood products according to predefined transfusion triggers which can be measured using coagulation tests. In a review of trigger guided transfusion during cardiovascular surgery, use of an algorithm significantly reduced patient exposure to allogeneic blood products in seven out of eight studies.144

Long turnaround times may preclude the use of some tests in emergency situations. Even in the absence of definitive evidence, implementation of POC assays appears rational if the alternative is haemostatic management guided by clinical judgement alone.119,120 A prospective study recently demonstrated superior turnaround times, and quality of assessment, with POC monitoring compared with PT and aPTT.31 Transfusion algorithms incorporating POC coagulation monitoring are effective in reducing blood loss, reducing exposure to allogeneic blood products and improving the safety and cost-effectiveness of haemostatic therapy in cardiac surgery.121,129,144

Perioperative coagulation monitoring is beneficial only if the results contribute to clinically effective decisions. Patients with similar conditions may receive different treatments if protocols and triggers for coagulation management are not in place.145 In a study of transfusion triggers used for bleeding management in OLT patients, substantial variability was observed in transfused quantities of FFP, platelets and cryoprecipitate when different monitoring assays were used.173 The authors concluded that further studies would be required to determine optimal monitoring procedures for guiding haemostatic intervention.

5.2 Evaluation of platelet function

Identification of platelet function is important for informing perioperative haemostatic management. There are several methods for assessing platelet function, each with its own limitations. The number of existing devices and their clinical validation is constantly evolving as is their utility in various settings. In this section, we will briefly address some of the existing commercial tests with sufficient clinical validation. However, separation of these devices into different subsets of sections does not exclude their application in other clinical settings.

Recommendations

We suggest preoperative platelet function testing only in addition to a positive bleeding anamnesis. 2C

We suggest that preoperative platelet function testing be used to identify decreased platelet function caused by medical conditions and antiplatelet medication. 2C

5.2.1 Which platelet function tests can be used preoperatively for identifying disturbances of primary haemostasis?

The Platelet Function Analyser (PFA-100)36, Siemens, Tarrytown, NY) test can be performed at the point-of-care to rapidly identify platelet defects before surgery.52,146 It has shown high sensitivity and specificity.
for platelet function screening performed preoperatively in patients with a positive bleeding history.\textsuperscript{52}

The PFA-100 test measures platelet response to agonists in citrated whole blood and can be used preoperatively at the point-of-care. However, the PFA-100 has demonstrated a relatively low predictive value for bleeding risk.\textsuperscript{146} In cardiac surgery patients, preoperative PFA-100 data have been shown to correlate with postoperative blood loss in some studies\textsuperscript{147} but not others.\textsuperscript{148}

The Cone and Plate(let) Analyser (CPA, Impact-R) test has been used successfully for screening of primary haemostasis abnormalities such as von Willebrand disease.\textsuperscript{149–151} The test can detect disturbances in primary haemostasis by measuring deposition of platelets from whole blood on to an artificial surface.

5.2.2 Preoperative platelet function testing in different clinical settings

5.2.2.1 Trauma

In a study of trauma patients, platelet function measured using the PFA-100 analyser showed a significant difference between survivors and non-survivors.\textsuperscript{152} To be useful in an emergency, a platelet function test needs to be applicable at the point-of-care and be capable of generating results quickly. A recent study used multiple electrode aggregometry (MEA, Multiplate) to assess platelet function of trauma patients on admission to the emergency room.\textsuperscript{153} ADPtest and TRAPtest values below the normal range were associated with increased mortality.\textsuperscript{153}

5.2.2.2 Cardiac surgery

The MEA ADPtest has provided results comparable with light transmittance aggregometry (LTA; considered as the ‘gold standard’ in platelet function testing) in coronary artery bypass graft (CABG) patients not taking antiplatelet therapies.\textsuperscript{154} Platelet dysfunction is a major cause of bleeding following cardiac surgery.\textsuperscript{155,156} Platelet activation (dysfunction) has been shown using Hemo-STATUS\textsuperscript{R} (Medtronic, Minneapolis, MN) testing during CPB.\textsuperscript{157}

MEA measurements taken preoperatively correlate closely with subsequent platelet transfusion requirements, more so than Impact-R tests.\textsuperscript{158} When selecting a platelet test for use during cardiac surgery, awareness of antiplatelet therapy is crucial because this may exacerbate surgical bleeding.\textsuperscript{47} As well as correlating with platelet transfusion requirements,\textsuperscript{158} the MEA ADPtest (performed 0.5–1 days before surgery) can predict postoperative bleeding in patients taking thienopyridines and undergoing CPB.\textsuperscript{159}

Three recently published studies (one retrospective and two prospective randomised clinical trials) have shown that perioperative platelet function testing using MEA or TEG Platelet Mapping in combination with ROTEM or TEG analysis is associated with reduced bleeding, reduced transfusion requirements, reduced costs and improved outcomes in cardiac surgery.\textsuperscript{119,120,160}

5.2.2.3 Liver surgery

Flow cytometry has been used to quantify platelet activation during liver transplantation, from the preoperative through to the postoperative period.\textsuperscript{161} Whole blood impedance aggregometry has been used to correlate platelet activation with ischaemia/reperfusion injury in paediatric liver transplantation.\textsuperscript{162}

Patients with liver disease may display altered platelet count\textsuperscript{163,164} and platelet function.\textsuperscript{165–167} In this setting, there is little evidence to indicate whether current diagnostic tests are useful for the preoperative identification of patients with increased perioperative bleeding risk.\textsuperscript{168}

Flow cytometry provides no evidence of systemic platelet activation during liver transplantation.\textsuperscript{161}

5.2.2.4 Obstetrics

Among pregnant women with type 1 Gaucher disease, abnormal CPA results have been associated with increased risk of peripartum haemorrhage.\textsuperscript{169} Furthermore, a study using a modified LTA assay found that patients with unexplained recurrent miscarriage have significantly increased platelet aggregation in response to arachidonic acid, providing a rationale for using aspirin in this setting.\textsuperscript{170}

5.2.3 Which platelet function tests can be used preoperatively for identifying the effects of antiplatelet therapy?

Before surgery the medical history should be taken and the patient’s exposure to antiplatelet medication should be determined.\textsuperscript{47,171} In patients with a positive bleeding anamnesis, full blood count, including examination of platelet count and size,\textsuperscript{172} and PFA-100 collagen-epinephrine and collagen-ADP\textsuperscript{52} are first level tests in preoperative evaluation. Antiplatelet therapy is associated with increased risk of perioperative bleeding but there is no consensus on the optimal timing of preoperative discontinuation. Reduced platelet function caused by antiplatelet medication can be quantified by evaluating the response to platelet agonists preoperatively.

Depending on the test reagent used, MEA is sensitive to aspirin, thienopyridines and glycoprotein (GP) IIb/IIIa inhibitors (e.g. abciximab), and has been used successfully for differential diagnosis.\textsuperscript{173–175} MEA provides differential diagnostic information by using platelet agonists as test reagents (e.g. collagen, arachidonic acid, ADP, thrombin receptor activator peptide [TRAP], von Willebrand factor [VWF]).\textsuperscript{173–175} However, clinical trials are needed to assess the value of MEA in perioperative monitoring of aspirin and clopidogrel.
5.2.4 Which platelet function tests can be used intraoperatively for monitoring the effects of surgery?
Platelet function decreases intraoperatively, irrespective of surgery type. Static tests which capture only a single time point do not reflect the dynamic nature of coagulopathic bleeding. For example, LTA is not suitable for intraoperative platelet function testing because of the long turnaround time. Point-of-care tests which can be performed rapidly are required, e.g., the HemoSTATUS platelet function test. MEA and PlateletWorks (clinical data are lacking for PlateletWorks). In general, a platelet count of ≥100 000 µL⁻¹ is needed for quantitative analysis.

5.2.4.1 Blood loss and synthetic colloid or crystalloid replacement
Platelet count decreases intraoperatively through major blood loss and dilution from volume resuscitation. Synthetic colloids or crystalloids may affect platelet function,²⁸⁸ although it has also been reported that these agents have no effect.²⁸⁹ Further studies are required to ascertain the effects of synthetic colloids and the most appropriate point-of-care tests to evaluate these effects.

5.2.4.2 Monitoring therapeutic interventions
Both PFA-100 and MEA have been used successfully to assess improvement in platelet function intraoperatively following administration of desmopressin.⁷¹,⁹³,¹⁸³ Platelet transfusion therapy can be guided and monitored using point-of-care testing, for example with the PFA-100 collagen and epinephrine (CEPI), and collagen and ADP (CADP) assays.¹⁸⁴ Following platelet transfusion, PFA-100 results provided a better indication of transfusion outcome than the previous ‘gold standard’, the corrected count increment (CCI).¹⁸⁴

5.2.4.3 Point-of-care testing immediately after surgery and on arrival at the intensive care unit
Following discontinuation of CPB, patients with severe aortic stenosis¹⁸³ or drug- or CPB-induced platelet dysfunction¹⁹⁹ may benefit from desmopressin. These patients can be identified using HemoSTATUS, a point-of-care test which measures platelet function independently of platelet count.¹⁸⁵ Upon arrival at the ICU, patients at risk of requiring platelet transfusion have been identified using MEA.¹⁸⁶

5.2.4.4 Which platelet function tests can be used postoperatively for monitoring haemostasis?
MEA has been used successfully to detect changes in platelet function after cardiac surgery.¹³⁴,¹⁸⁷ Platelet function testing (e.g., PFA-100) can be used to detect changes in platelet reactivity after surgery and to monitor the effectiveness of antiplatelet medication. However, evidence for the postoperative use of platelet function tests is limited.

5.2.4.5 Are patient outcomes improved by algorithms which incorporate platelet function testing for intraoperative haemostatic monitoring?
Both laboratory and point-of-care platelet function tests are included in some algorithms for managing perioperative bleeding¹⁸⁸,¹⁸⁹ but there is currently insufficient evidence to answer this question definitively.

6 ANAEMIA MANAGEMENT
6.1 Preoperative correction of anaemia
6.1.1 Introduction
Perioperative anaemia increases the risk of numerous complications such as cardiac events, pneumonia and postoperative delirium.¹⁹⁰,¹⁹¹ Associations between anaemia and higher rates of both morbidity and mortality are well established for patients undergoing cardiac surgery.¹⁹²,¹⁹³ A recent, large cohort study demonstrated that these associations also apply to non-cardiac surgery; the odds ratio for mortality among patients with anaemia versus those without was 1.42.¹⁹⁴ Preoperative anaemia has been shown to be predictive for perioperative transfusion of allogeneic blood products such as red blood cells, which itself carries a significant risk of adverse events and mortality.¹⁹²,¹⁹⁵,¹⁹⁶ There is some tolerance to postoperative anaemia among patients without cardiovascular disease, but for each 1 g dl⁻¹ decrease in postoperative haemoglobin concentration below 7 g dl⁻¹, mortality has been shown to increase by a factor of 1.5.¹⁹¹ Estimates of the prevalence of anaemia in surgical patients range widely, from 5% to 76%.¹⁹⁷ High rates have been reported in cancer patients (e.g., breast cancer, colon cancer), while lower rates have been observed in orthopaedic patients.¹⁹⁷,¹⁹⁸

Allogeneic blood transfusion has long been used for correcting perioperative anaemia. However, there is a
6.1.2 Preoperative assessment

Recommendation
We recommend that patients at risk of bleeding are assessed for anaemia 4–8 weeks before surgery. 1C

This recommendation is essentially empirical. There are no trials proving whether assessment of patients has an impact on their outcomes, or proving the optimum time before surgery when patients should be assessed. However, as interventions have been shown to be effective among patients with anaemia, it is valuable to assess patients before elective surgery to allow the possibility of treating anaemia before the procedure, and the period of 4–8 weeks provides enough time for treatment to take effect.

Recommendation
If anaemia is present, we recommend identifying the cause (e.g. iron deficiency, renal deficiency or inflammation). 1C

This is another empirical recommendation. There are numerous possible causes of anaemia, and accurate diagnosis enables appropriate treatment to be administered before surgery. There are no clinical trials comparing outcomes among patients with or without accurate diagnosis of their anaemia.

Accurate diagnosis requires a work-up after determination of a low haemoglobin concentration. 191,201,202 Serum ferritin concentration below 30 \( \mu \text{g} \text{l}^{-1} \) signifies nutritional iron deficiency for which iron therapy is administered, although referral to a gastroenterologist may be considered to rule out malignancy. 191 A serum ferritin concentration of 30–100 \( \mu \text{g} \text{l}^{-1} \) signifies possible iron deficiency, while a concentration above 100 \( \mu \text{g} \text{l}^{-1} \) indicates that anaemia is related to causes such as chronic disease (renal or otherwise) or inflammation. In this case, further tests are needed (e.g. assessment of renal function and vitamin B12/folic acid concentrations) to ascertain the diagnosis. 191,201,202

6.1.3 Preoperative treatment

Recommendation
We recommend treating iron deficiency with iron supplementation (oral or intravenous). 1B

Most (though not all) studies report that preoperative oral iron supplementation is effective in raising haemoglobin concentration and decreasing perioperative transfusion. Two controlled studies have investigated the effects of at least 2 weeks of preoperative oral iron supplementation. The first was a retrospective comparison of colorectal surgery patients with anaemia who either received or did not receive iron supplementation. 203 The second was a randomised, placebo-controlled trial of oral ferrous sulphate, also performed in the colorectal surgery setting, with patients recruited whether or not they had anaemia. 204 In both of these studies, iron supplementation produced a significant increase in haemoglobin concentration, as well as significantly decreased blood transfusion rates during surgery.

The efficacy of oral iron has also been demonstrated in patients with anaemia. In a study by Cuenca et al., 205 oral iron supplementation was taken for 30–45 days preoperatively by knee replacement surgery patients. Reduced transfusion of allogeneic blood products was observed, compared with a retrospective control group not receiving iron. This was the case for patients with anaemia (haemoglobin [Hb] <13.0 g dl\(^{-1}\)) as well as those with higher haemoglobin concentrations. In another study, a significant 1.1 g dl\(^{-1}\) increase in haemoglobin concentration was observed in response to 4 weeks preoperative treatment with oral iron supplementation among hip or knee replacement patients with anaemia (Hb <12.0 g dl\(^{-1}\) before iron supplementation). 206 Furthermore, Quinn et al. 207 showed in a prospective observational study that oral iron sulphate (200 mg, three times daily for a median of 39 days) increased haemoglobin concentration by 1.73 g dl\(^{-1}\) (\(P < 0.001\)) among colorectal cancer surgery patients presenting with preoperative anaemia.

In contrast to the results described above, one prospective, observational study reported that oral iron supplementation is not effective for increasing haemoglobin concentration. 208 Eighty seven patients with haemoglobin concentrations between 10.0 and 15.0 g dl\(^{-1}\) received iron sulphate (300 mg three times daily) for at least 3 weeks before hip or knee arthroplasty, and a 0.14 g dl\(^{-1}\) decrease in haemoglobin concentration (\(P = 0.015\) ) was observed.

Although oral iron supplementation may be suitable for a high proportion of patients, there are some in whom intravenous iron should be considered, e.g. for patients unable to tolerate oral iron (usually due to gastrointestinal side effects). 190

Among women with complicated pregnancy or complicated childbirth, intravenous iron sucrose has been shown
to increase haemoglobin concentration by 2.1 g dl⁻¹ within 7 days of administration. A comparator group of patients received oral iron supplementation, and these women showed no increase in haemoglobin concentration (possibly because of the short time period). In another study of intravenous iron sucrose, administered preoperatively to patients scheduled for orthopaedic surgery, a significant increase in haemoglobin concentration was observed. Munoz et al. reported in a prospective, observational study that intravenous iron sucrose (mean dose 1000 mg), administered over 3–5 weeks to patients with preoperative anaemia, increased haemoglobin concentration by 2.0 g dl⁻¹ ($P < 0.001$), resolving anaemia in 58% of patients.

In contrast to these results, a randomised controlled trial performed in 60 patients undergoing colorectal cancer resection reported that intravenous iron administered 14 days before surgery had no impact on haemoglobin concentration, in comparison with placebo.

Intravenous iron may provide a greater increase in haemoglobin concentration than oral iron. In a randomised, prospective study, women with anaemia caused by menorrhagia (Hb < 9.0 g dl⁻¹) were treated with intravenous iron sucrose (total calculated iron deficit divided into two ampoules, three times per week) or oral iron protein succinylate daily. Treatment was administered during the 3 weeks before elective surgery, and a significantly greater increase in haemoglobin concentration was observed in the intravenous group (3.0 vs. 0.8 g dl⁻¹, $P < 0.0001$).

One study has shown that preoperative intravenous iron can reduce transfusion among patients undergoing surgery for trochanteric hip fracture. The transfusion rate was 39.1% among patients receiving intravenous iron, compared with 56.7% in a retrospective control group. In contrast, a randomised controlled trial performed in patients undergoing colorectal cancer resection showed that transfusion rates were no different between patients receiving preoperative intravenous iron or placebo.

Intravenous iron appears to be well tolerated. Older preparations of iron for intravenous administration were associated with a risk of anaphylactic reactions. However, a number of studies performed in recent years have reported a lack of adverse events associated with intravenous iron, while others have reported favourable tolerability. Today’s intravenous iron preparations may therefore be considered as being much safer than those available in previous decades, although the possibility of adverse events such as hypotension, arthralgia, abdominal discomfort and back pain remains.

Other safety concerns with intravenous iron include infection and cancer progression, but prospective data confirm lack of association with bacteraemia and there are no data to confirm increased risk of cancer progression.

Recommendation If iron deficiency has been ruled out, we suggest treating anaemic patients with erythropoietin-stimulating agents.

Erythropoietin reduces transfusion of allogeneic blood products, although not in patients with near normal haemoglobin concentrations and not in patients undergoing colorectal cancer surgery. In a meta-analysis of cardiac surgery and orthopaedic surgery studies, reduced perioperative transfusion of allogeneic blood products was observed among patients receiving erythropoietin. The odds ratio for the proportion of patients transfused with allogeneic blood with erythropoietin was 0.36 ($P = 0.0001$) in orthopaedic surgery and 0.25 (not significant) in cardiac surgery. The dose of erythropoietin had no statistically significant effect on the odds ratio. Another meta-analysis examined the effect of erythropoietin on allogeneic blood transfusion among patients undergoing cardiac surgery. For patients not undergoing autologous blood transfusion, the relative risk of allogeneic blood transfusion with erythropoietin was 0.53 ($P < 0.01$), and for those undergoing autologous blood transfusion, the relative risk was 0.28 ($P < 0.001$). In contrast to these meta-analyses, a Cochrane review of pre- and perioperative erythropoietin among colorectal cancer surgery patients reported no significant effect on the proportion of patients receiving allogeneic blood transfusion. A meta-analysis of studies of erythropoietin-stimulating agents in a broader population of cancer patients showed that these agents can reduce the need for red blood cell transfusions with no impairment of survival. However, in this context, erythropoietin-stimulating agents are recommended only according to the label (i.e. start treatment only if haemoglobin concentration is <11.0 g dl⁻¹, and discontinue treatment when the haemoglobin concentration increases to 12.0–13.0 g dl⁻¹), because when used off-label (i.e. to achieve higher concentrations of haemoglobin), they are associated with reduced survival among cancer patients.

Individual randomised controlled trials have reported significant reductions in allogeneic blood product transfusions among patients undergoing orthopaedic surgery, cardiac surgery and surgery for colorectal cancer or other gastrointestinal tract malignancies. However, the effect of erythropoietin on transfusion rates has been shown to be non-significant in hip replacement patients with near normal preoperative haemoglobin concentrations, radical prostatectomy patients with near normal haematocrit and colorectal cancer patients with anaemia.

Based on the available data, erythropoietin-stimulating agents have been recommended for orthopaedic surgery patients with anaemia, in whom nutritional deficiencies are absent or have been corrected.
Two large, randomised controlled trials have shown the potential for erythropoietin to increase haemoglobin concentration. The first, involving 695 orthopaedic surgery patients with preoperative haemoglobin concentrations between 10.0 and 13.0 g dL⁻¹, showed that preoperative epoietin alpha produced higher haemoglobin concentrations from the day of surgery until discharge from hospital (P < 0.001). In the second study, involving 204 colorectal cancer surgery patients, those receiving preoperative epoietin alpha 300 IU kg⁻¹ per day showed significantly higher haemoglobin concentrations than controls on the day before and the day after surgery. Significant increases in haemoglobin concentrations have been reported in several other randomised controlled trials of preoperative erythropoietin performed in patients undergoing orthopaedic surgery and hysterectomy.

TREATMENT WITH EPOIETIN ALPHA (40,000 IU ON PREOPERATIVE DAYS 21, 14, 7 AND 1) WAS SHOWN IN A PROSPECTIVE, OBSERVATIONAL STUDY TO INCREASE HAEMOGLOBIN CONCENTRATIONS IN ORTHOPAEDIC SURGERY PATIENTS BY 2.0 g dL⁻¹ AND 1.8 g dL⁻¹ IN PATIENTS AGED ≥65 YEARS AND <65 YEARS, RESPECTIVELY. In a second study of orthopaedic surgery patients performed by the same group, a similar increase in haemoglobin concentration was observed in response to similar preoperative treatment with epoietin alpha. Another prospective, non-randomised study of preoperative recombinant human erythropoietin reported dose-dependent increases in haemoglobin concentrations among gynaecological surgery patients both before surgery and on discharge. In an earlier study, epoietin alpha at a dose of 600 IU kg⁻¹ weekly provided a larger increase from baseline in haemoglobin concentration compared with a daily dose of 300 IU kg⁻¹.

There may be a risk of thrombotic complications with erythropoietin-stimulating agents, and prophylaxis for deep vein thrombosis (DVT) should be considered. Early studies did not show an increased risk of DVT among patients receiving erythropoietin. A meta-analysis published in 1998 reported a lack of ‘convincing evidence’ that erythropoietin causes thrombotic complications, although an increased occurrence of such events was noted in some studies with limited patient numbers. More recent studies of erythropoietin (or epoietin alpha), designed primarily to assess efficacy, have suggested a lack of significant safety concerns. In a Cochrane review of erythropoietin in colorectal cancer surgery reported no significant difference in thrombotic events between patients receiving erythropoietin and controls.

However, data from an open-label study involving 681 spinal surgery patients showed a clear increase in the incidence of DVT among recipients of erythropoietin. Similarly, in a randomised, open-label study of epoietin alpha versus standard care involving 680 spinal surgery patients, DVT, diagnosed either by Doppler imaging or by adverse event reporting, occurred in a higher proportion of patients in the epoietin alpha group. Such data prompted the Food and Drug Administration (FDA) to require a warning to be added to the package inserts for erythropoietin and darbepoietin alpha, stating that DVT prophylaxis should be considered.

**Recommendation**

If autologous blood donation is performed, we suggest treatment with erythropoietin-stimulating agents in order to avoid preoperative anaemia and increased overall transfusion rates. A meta-analysis has shown that autologous blood donation reduces transfusion of allogeneic blood products, but that it increases overall transfusion rates. Other studies suggest that autologous blood donation does not necessarily reduce allogeneic blood transfusion. In a large retrospective study involving 541 spinal surgery patients, those undertaking autologous blood donation had 1/25 of the chance of requiring allogeneic blood products compared with control patients who did not donate. However, the overall transfusion rate was higher in the autologous donation group. These results reflect those of a Cochrane meta-analysis which concluded that, although autologous blood transfusion reduces allogeneic blood transfusion, overall transfusion (including autologous blood) is increased. A randomised controlled trial performed in 32 cardiac surgery patients reported that autologous blood donation was associated with decreased allogeneic blood transfusion (0.59 vs. 5.01 U per patient). However, this result may have been influenced by the fact that blood donation patients also received 3 weeks of treatment with recombinant human erythropoietin.

Evidence from other studies suggests that autologous blood donation may not reduce patients’ exposure to allogeneic blood products. In a prospective study conducted in patients undergoing hip replacement surgery, there was no significant difference in exposure to allogeneic blood products between autologous donors and non-donors. In a retrospective study by Jawan et al., performed to compare liver resection patients donating their own blood preoperatively with those not doing so, none of the patients required perioperative transfusion of blood products. Consequently, all predonated blood was discarded. In another retrospective study, performed in knee/hip arthroplasty patients, autologous blood donation was associated with increased perioperative transfusion and the authors suggested that autologous donation may create a ‘self-defeating cycle of blood donation followed by blood transfusion’. Autologous blood transfusion may be considered for patients with multiple antibodies (for whom donor blood may be difficult to obtain).
Autologous blood donation increases preoperative anaemia. In a retrospective study of patients scheduled for knee replacement surgery, haemoglobin concentrations before autologous blood donation were compared with those immediately before surgery.\(^{200}\) The percentage of patients with a haemoglobin concentration in the range of 10–13 g dl\(^{-1}\) (at high risk for perioperative transfusion) increased from 26.2% to 55.7%. In the liver resection study by Jawan et al.,\(^{248}\) significantly lower perioperative haemoglobin concentrations were observed in autologous blood donation patients than in non-donors. Another comparative retrospective study reported that patients undertaking autologous blood donation had significantly lower haemoglobin concentrations before surgery than patients not making autologous donations; the authors concluded that ‘autologous blood donation induced preoperative anaemia’.\(^{244}\)

Randomised controlled trials indicate that erythropoietin may be used to increase the proportion of patients able to make autologous blood donations (assuming a minimum haematocrit threshold for making a donation)\(^{226}\) and to reduce the extent to which autologous blood donation lowers haemoglobin concentration.\(^{250}\)

One randomised controlled trial assessed prophylactic administration of autologous fresh frozen plasma (FFP) after CPB in patients undergoing coronary artery bypass surgery.\(^{251}\) This intervention failed to produce significant reductions in transfusion or blood loss compared with administration of hydroxyethyl starch.

Autologous platelet-rich plasma may be superior to autologous whole blood in decreasing transfusion of allogeneic blood products. Farouk et al.\(^{252}\) performed a randomised trial comparing administration of platelet-rich plasma with acute normovolaemic haemodilution in patients undergoing open heart surgery. Platelet-rich plasma produced a significant decrease in transfusion of blood products compared with acute normovolaemic haemodilution.

### 6.1.3 Other possible treatment approaches

Combined use of intravenous iron, erythropoietin, vitamin B\(_{12}\), folic acid, and restrictive transfusion may reduce transfusion requirements. Limited evidence suggests that patients with anaemia might benefit from combination therapy. In a prospective study, patients undergoing total knee replacement received intravenous iron sucrose and, if haemoglobin concentration remained <13.0 g dl\(^{-1}\), additional erythropoietin. These measures, together with restrictive transfusion, ‘seem to reduce allogeneic blood transfusion’, although there was no control group.\(^{215}\) Retrospective assessment of a similar approach to managing anaemia in hip fracture patients showed a reduction in transfusion compared with oral iron or intravenous iron only.\(^{253}\) Haemoglobin concentrations 48 h after surgery were higher in the oral iron group, but this difference was not apparent 7 days after surgery.

In a retrospective study, intraoperative cell salvage (ICS) was used together with autologous blood donation in hip surgery patients, and homologous blood transfusion was avoided in all 154 patients.\(^{254}\) Donation volumes were 800 ml for patients undergoing total hip arthroplasty and 1200 ml for patients undergoing rotational acetabular osteotomy.

### 6.2 Intra- and postoperative optimisation of macro- and microcirculation

#### 6.2.1 Introduction

Massive bleeding affects delivery of blood to organs and tissues (due to hypovolaemia), as well as the oxygen-carrying capacity of blood (due to anaemia). Because normal haemoglobin concentrations provide a large oxygen carrying capacity, priority goes to intravascular volume replacement with plasma substitutes devoid of red blood cells (RBCs). Transfusion of RBCs is required only when the haemoglobin concentration decreases to levels at which overall nutrient demands cannot be met. This section focuses on rational fluid substitution techniques and anaemia management in patients suffering severe haemorrhage.

#### 6.2.2 Evidence-based medicine and perioperative fluid therapy

Creating reliable and generally acceptable outcome based evidence on perioperative fluid management is currently not feasible due to a lack of controlled studies, the limited representation of clinical scenarios and the absence of a consistent terminology. Several studies have evaluated the impact of perioperative fluid therapy on patient outcomes.\(^{255–268}\) However, few qualify to serve as a basis for recommendations. The better studies have been performed in abdominal surgery,\(^{256,263–265,268}\) where perioperative fluid needs may differ considerably from other surgical procedures.\(^{269}\) Patients at high-risk are often excluded, even if they represent the typical collective.\(^{270}\) The impact of perioperative fluid management on outcome cannot be isolated from other interventions\(^{271}\) and only two prospective trials included details of therapeutic strategy beyond fluid therapy.\(^{261,262}\) Perioperative fluid management must be embedded in a larger perioperative therapeutic concept in order to impact on patient outcome.

#### 6.2.3 Optimising macrocirculation

##### 6.2.3.1 Preload optimisation

**Recommendation**

*We recommend aggressive and timely stabilisation of cardiac preload throughout the surgical procedure, as this appears beneficial to the patient.* \(^{1B}\)

Hypovolaemia decreases cardiac output and tissue oxygen supply. Both the extent and duration of tissue hypoperfusion determine the severity of cellular damage and should be kept to a minimum with timely...
volume substitution. Two recent meta-analyses concluded that a goal-directed approach to maintaining tissue perfusion reduces mortality, postoperative organ failure and surgical complications in high-risk surgical patients.\textsuperscript{272,273}

**Recommendation**

We recommend the avoidance of hypovolaemia with crystalloids or colloids to a level exceeding the interstitial space in steady state, and beyond an optimal cardiac preload.\textsuperscript{1B}

The relationship between risk and total volume transfused appears to follow a U-shaped curve (infusing too much can be as deleterious as infusing too little).\textsuperscript{274} Fluid excess can have a negative impact on cardiac, pulmonary and bowel function, wound healing and water and sodium regulation.\textsuperscript{275} Surgery causes inflammation\textsuperscript{276} and the corresponding response of mediators causes local tissue oedema.\textsuperscript{277} Artificial hypovolaemia predisposes patients to interstitial oedema, which appears to be associated with perioperative mortality.\textsuperscript{278}

**Recommendation**

We recommend against the use of central venous pressure and pulmonary artery occlusion pressure as the only variables to guide fluid therapy and optimise preload during severe bleeding; dynamic assessment of fluid responsiveness and non-invasive measurement of cardiac output should be considered instead.\textsuperscript{1B}

To determine the amount of fluid required, high fidelity monitoring is necessary. The monitored variable should predict whether or not a fluid bolus will increase cardiac output.

Central venous pressure (CVP) remains the most widely used clinical marker of volume status, despite numerous studies showing no association between CVP and circulating blood volume.\textsuperscript{279} Several studies have demonstrated that dynamic parameters such as stroke volume variation (SVV) or pulse pressure variation (PPV) provide better prediction of fluid responsiveness in mechanically ventilated patients with a normal heart rhythm. Fluid challenges and the leg-raising test represent simple and valid alternatives;\textsuperscript{280} no data prove the superiority of substitution regimens guided by SVV or PPV.

The most extensively studied and successfully used method to maximise cardiac preload is the oesophageal Doppler device.\textsuperscript{259,281–286}

**6.2.3.2 Delayed and low-volume resuscitation techniques**

The general implementation of a delayed or low-volume resuscitation protocol for the severely bleeding patient cannot be recommended at this time. However, such a protocol may be applied for specific lesions, provided that surgical control of bleeding is imminent.

**6.2.4 Considerations for microcirculation**

**6.2.4.1 Compartmental fluid dynamics**

Basic physiological principles during steady state assume the presence of a cell membrane, quantitatively impermeable to electrolytes, proteins and colloids, and a vascular barrier which retains proteins and colloids, but is freely permeable to electrolytes and other small solutes. Water flows passively across all compartments and distributes according to the amount of osmotically and oncotically active substances. This leads to the following primary distribution pattern: free water evenly across all the compartments (intravascular volume effect negligible); isotonic crystalloids within the extracellular fluid space (intravascular volume effect around 20%); and iso-oncotic colloids and proteins within the intravascular space (intravascular volume effect around 100%).\textsuperscript{276,279,287–289} Thus, the infusion of crystalloids has been associated with substantial interstitial oedema (unpublished observations).

**6.2.4.2 Crystalloids versus colloids**

**Recommendation**

We suggest the replacement of extracellular fluid losses with isotonic crystalloids in a timely and protocol based manner.\textsuperscript{2C}

Compared with crystalloids, haemodynamic stabilisation with iso-oncotic colloids, such as human albumin and hydroxyethyl starch, causes less tissue oedema.\textsuperscript{C}

Losses from the extracellular space occur continuously via perspiration and urinary output. During fasting, these losses are not replaced and substitution is required. Healthy adults perspire around 0.5 ml kg\textsuperscript{-1} h\textsuperscript{-1}, and the corresponding value during major abdominal surgery is ≤1 ml kg\textsuperscript{-1} h\textsuperscript{-1}.\textsuperscript{290} This loss, together with urinary output, should be replaced. There is no evidence that additional administration of crystalloid preserves organ function.

In healthy patients, stabilisation of cardiac preload with iso-oncotic colloids such as human albumin and hydroxyethyl starch causes less tissue oedema than do crystalloids. It is unclear whether this translates into any clinical outcome benefit. The safety profile of artificial colloids is unconfirmed.

The most important colloid solutions are human albumin, hydroxyethyl starch, gelatin and dextran. The volume effect of gelatin preparations appears inferior to that of starch or albumin preparations.\textsuperscript{291–293} However, a recent review concluded that such effects are temporary and do not translate into different clinical outcomes.\textsuperscript{292} While side effects of colloids remain a concern, a recent systematic review failed to show any significant safety differences between the available colloids.\textsuperscript{294}

**6.2.4.3 Chlorine balanced solution**

**Recommendation**

We suggest the use of balanced solutions for crystalloids and as a basic solute for iso-oncotic preparations.\textsuperscript{2C}
6.2.4.5 Oxygen fraction

Recommendation
We recommend that inspiratory oxygen fraction should be high enough to prevent arterial hypoxaemia in bleeding patients, while avoiding excessive hyperoxia (PaO₂ > 26.7 kPa [200 mmHg]). 1C

The use of high inspiratory oxygen fractions during artificial ventilation (hyperoxic ventilation, HV) is traditionally advised for emergencies on the basis that severe arterial hypoxaemia potentially endangers oxygen delivery. However, it has been demonstrated that the side effects of HV (e.g. vasoconstriction) may worsen patient outcomes. 302,303 Overall, current evidence supports the use of HV to achieve physiological arterial oxygen partial pressures during haemorrhagic shock.

6.2.4.6 Monitoring tissue perfusion

Recommendation
We recommend repeated measurements of a combination of haematocrit/haemoglobin, serum lactate, and base deficit in order to monitor tissue perfusion, tissue oxygenation and the dynamics of blood loss during acute bleeding. These parameters can be extended by measurement of cardiac output, dynamic parameters of volume status (e.g. stroke volume variation, pulse pressure variation) and central venous oxygen saturation. 1C

There is no easily applicable tool for monitoring blood volume in a clinical setting. Consequently, surrogate parameters (e.g. haematocrit/haemoglobin, central venous pressure, pulmonary capillary wedge pressure, stroke volume variation, pulse pressure variation, serum lactate concentration, base deficit) are used. Some of these parameters have been demonstrated to be inappropriate, such as central venous pressure and pulmonary capillary wedge pressure, while others require specific monitoring tools which are not widely available, including stroke volume variation and pulse pressure variation with special monitors.

Due to low sensitivity and specificity, haematocrit and haemoglobin concentration should not be used as exclusive measures to monitor the extent of acute blood loss. 304,305 However, since haemoglobin concentration is one important determinant of systemic oxygen delivery, it should be monitored regularly.

Serum lactate concentration and base deficit reflect global tissue perfusion and oxygenation in haemorrhagic shock. Although both can be influenced by many different factors, their concentrations can be used to determine severity of haemorrhagic shock, guide substitution and transfusion protocols 306,307 and potentially predict survival. 308 However, it has not yet been shown whether the outcome of severe bleeding can be improved if volume resuscitation is guided by serum lactate concentration and base deficit. 309

Central venous oxygen saturation (ScvO₂) is used in sepsis to guide volume therapy and other measures to optimise oxygen delivery. 310 Although it has been demonstrated that ScvO₂ reflects blood loss in the early stages of haemorrhagic shock, 311 circulation is centralised during severe haemorrhage, which raises ScvO₂. Therefore, ScvO₂ values during severe haemorrhage must be interpreted cautiously. 312

6.3 Transfusion of labile blood products

6.3.1 Infectious risk of allogeneic blood components

Recommendation
We recommend that all countries implement national haemovigilance quality systems. 1C

Although tremendous progress has been made regarding the safety of blood components, there remains a residual
risk of transfusion-related infection. Most transfusion services in Europe and the USA require that all donations are screened for hepatitis B and C viruses (HBV; HCV), human immunodeficiency virus (HIV) and syphilis. Universal testing for other infectious agents such as West Nile Virus, malaria, Chagaz disease and human T-cell lymphphotropic virus (HTLV) is not justified because of their restricted geographical distribution; instead, donor screening is employed. Potential donors are asked questions on travel history, drug abuse, sexual behaviour, etc; however, residual risks remain. There is also a risk that laboratory testing of donated blood is not effective. There is usually a period during which the donation is infectious but will screen negative because the infectious marker is not present at detectable levels. Shortening of this ‘window period’ is a major target of all screening programmes.

In addition to known infectious agents, there is also the threat of new or emerging pathogens. Due to increased travel and spread of mosquitoes, the most important emerging threats are the mosquito borne Dengue, Chikungunya and Zika viruses.

Bacterial contamination is another issue of transfusion practice. Since the introduction of disposable collection systems, the incidence of bacterial contamination has decreased dramatically. However, platelets, which are stored at room temperature and suspended in plasma, still present a significant risk. The greatest risk of contamination occurs during collection, because bacteria are present on the donor’s skin. Disinfection techniques have improved, and small sideways collectors used to collect the first 30 ml of donated blood reduce the contamination risk. Additional measures include the use of closed systems and improvements in processing area hygiene.

Most countries have developed a national haemovigilance system to identify adverse outcomes of transfusion. Introduced in 1996, the UK Serious Hazards of Transfusion (SHOT) scheme involves compulsory reporting of all transfusion-related incidents. The latest SHOT report (2009) demonstrated a tremendous reduction in serious outcomes compared with the first report (1996). However, links between infection and transfusion are not always made.

**Recommendation**

*We recommend a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products.*

One of the most effective ways to reduce transfusion related infection is to introduce a restrictive transfusion protocol, i.e. transfuse only what is really necessary (RBCs, plasma or platelets) and only when it is really necessary.

The Transfusion Requirements in Critical Care (TRICC) multicentre randomised controlled trial compared restrictive transfusion (Hb concentration maintained at 7–9 g dl\(^{-1}\)) with liberal transfusion (Hb concentration maintained at 10–12 g dl\(^{-1}\)). 30-day mortality was higher with liberal transfusion. A recent Cochrane review of RBC transfusion triggers included 17 RCTs. A lower RBC transfusion trigger reduced postoperative infection by 24%, with no adverse effects on mortality, cardiac morbidity or length of hospital stay. Transfusion in acute coronary syndrome has been associated with increased mortality, except in the elderly where it reduces fatality if the haematocrit is below 30%.

**Recommendation**

*We recommend photochemical pathogen inactivation with amotosalen and UVA light for platelets.*

Pathogen inactivation kits have recently been licensed for plasma and platelets, but not for RBCs. Such technology is probably most important for new and emerging infectious threats or in situations in which testing is only partially effective (e.g. bacterial contamination of platelet products).

Solvent and detergent (SD) was the first pathogen inactivation technique, introduced for plasma in the early 1990s. The process is based on disruption of the viral envelope but is only effective against lipid-enveloped viruses and is not applicable for use with RBCs or platelets.

More recently, the combination of photosensitisers and white or ultraviolet light has been developed to act at the nucleic acid level. The principle of this approach is that viral and bacterial pathogens (except prions) need genetic material to be viable, whereas therapeutic blood components do not. The Intercept Blood System (Cerus Corporation, Concord, CA) for platelets and plasma uses photoactive amotosalen to irreversibly block the replication of DNA and RNA. The Systolic Blood Pressure Intervention Trial (SPRINT) examined the therapeutic efficacy and safety of platelets treated with amotosalen and ultraviolet light. This RCT showed that the use of pathogen-inactivated platelets is not associated with increased bleeding and confirmed a lack of either toxicity or neoantigen formation associated with this photochemical process.

Another photoactivation method applied to plasma is methylene blue combined with visible light. Few RCTs have assessed this method, and there are concerns over reduced efficacy of methylene blue treated plasma in patients with thrombotic thrombocytopenic purpura.

Photoinactivation is less applicable to RBCs because of their high optical density, which impairs penetration of photoactive molecules. Nevertheless, research with riboflavin is ongoing.

**Recommendation**

*We recommend that labile blood components used for transfusion are leukodepleted.*
The infectious risk of leukocyte-mediated viruses (cytomegalovirus [CMV], HTLV, HIV) may be reduced by prestorage removal of leukocytes from blood components. For RBCs, this can be achieved by using dedicated filters, while for platelet products, leukocytes are removed during the collection process via apheresis. Third-generation leukocyte depletion filters appear effective in preventing primary CMV infection in neonates, adult cancer patients and bone marrow transplant patients. Leukodepletion does not remove all leukocytes, but there is evidence that CMV seronegative and leukoreduced blood components are equivalent, provided that \( \leq 5 \times 10^8 \) white cells remain in the product transfused.\(^{328}\)

Universal leukodepletion of blood components was introduced in the UK in 1998 on the basis that it reduces the risk of variant Creutzfeldt-Jacob disease (vCJD) transmission.\(^{329}\)

Another benefit of prestorage leukodepletion is prevention of febrile non-haemolytic transfusion reactions (FNHTRs). These are the most frequent adverse reactions following transfusion of blood components, with an incidence of 1% with non-leukodepleted RBCs and 5–10% with platelets.\(^{330}\) The main cause of FNHTRs is antibodies in the recipient being directed against antigens on the donor’s white cells and platelets.\(^{331}\) Leukoreduction of transfused blood components to \(<5 \times 10^6\) leukocytes per unit has been shown to significantly reduce the occurrence of FNHTRs.\(^{329,332}\)

### 6.3.2 Immuneological complications of blood transfusion

The SHOT report is a haemovigilance data collection system involving all UK hospitals. Since it began, 6653 transfusion-related adverse events have been recorded. In the first SHOT report (1996–1997) there were 141 reports, 36 cases of major morbidity and 12 deaths, representing a serious outcome percentage of 34% (48/141). By 2009, the serious outcome percentage had decreased to 6.7% (86/1279). Two hundred and eighty two reports (22%) were attributable to incorrect blood component transfusion (e.g. wrong ABO and Rh group).\(^{320}\) It is estimated that approximately 1 in 30 000 transfused RBC units are ABO incompatible and that around 1 in 500 000 deaths are due to ABO incompatibility. This is ten-fold higher than the risk of acquiring HIV infection by transfusion in the UK.\(^{337}\)

Other immune mediated causes of transfusion-related morbidity and mortality identified by SHOT include haemolytic transfusion reactions, FNHTRs, allergic and anaphylactic reactions, transfusion-related acute lung injury (TRALI) and transfusion-associated graft-versus-host disease (TA-GVHD).

**Recommendation**

_We recommend that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions._ IC

Haemolytic transfusion reactions (HTRs) are typically caused by transfusion of RBCs carrying antigens to which the recipient has significant alloantibodies. The vast majority of cases are attributable to bedside clerical/procedural errors, either when taking samples for pre-transfusion screening or before the administration of the blood component.\(^{333}\)

The pathogenesis of HTRs may be related to complement activation after IgM antibodies have been fixed (severe acute HTRs), or to IgG antibodies (e.g. anti-D, anti-K) in patients who have been sensitised either by pregnancy or by previous transfusion (less severe acute HTRs; approximately 1 in 25 000 transfused units of RBCs).\(^{334}\) Onset of HTRs can be delayed by approximately 1 week following transfusion, by anamnestic or secondary immune responses in previously primed patients.

The first signs of both acute and delayed HTRs are fever and chills.\(^{335}\) Hypotension, tachycardia, nausea and vomiting, loin and chest pain, and renal failure may be associated with acute HTRs or, less commonly, with delayed HTRs. Anaesthesia may mask the typical symptoms of renal failure and red cell destruction may be noted by the presence of haemoglobinuria and excessive bleeding because of disseminated intravascular coagulation. Haemoglobinuria, haemoglobinuria, jaundice and DIC may also occur with acute HTRs, in relation to intra- or extravascular haemolysis.

The most frequent cause of intravascular HTRs is ABO incompatibility attributable to procedural errors. Most deaths occur with transfusion of group A or group B to group O recipients.

Occasionally HTRs may be associated with transfusion of plasma or even platelets. Here, transfusion of group O plasma containing antibodies against A or B antigens on the recipient’s RBCs leads to haemolysis.

Rarely, incompatibility between RBCs from one donor and the plasma from another donor causes haemolysis in the recipient (interdonor incompatibility).

The American Association of Blood Banks guidelines recommend that if an HTR is suspected, transfusion must be stopped immediately.\(^{330}\) This is because the severity of haemolysis is related to the volume of incompatible blood transfused. Treatment should be guided by the clinical manifestations. For mild symptoms, careful observation may suffice, but severe reactions demand vigorous therapy. For example, exchange transfusion may be lifesaving in cases of ABO incompatibility and severe haemolysis. Renal failure may be prevented by maintaining urine output with fluids and diuretics. Pressure support may be needed in the presence of hypotension.
and shock, while DIC should be managed according to local protocols.

Febrile non-haemolytic transfusion reactions (FNHTRs) are defined as an increase in body temperature of ≥1°C occurring in association with the transfusion of blood components and not explained by other aspects of the patient’s medical condition. Chills, rigor and discomfort may be present and usually respond well to antipyretic agents. Because fever is present in other transfusion reactions, such as acute HTR, TRALI and bacterial contamination, diagnosis of FNHTR is made by exclusion. If in doubt, a direct antiglobulin test should be performed and concentrations of free haemoglobin should be assessed.

Allergic and anaphylactic reactions develop as a type 1 hypersensitivity response to plasma proteins present in transfused blood components, meaning that an immediate allergic reaction follows any subsequent contact with the antigen to which the recipient has been previously sensitised. Crosslinking of antigen with surface IgE stimulates degranulation of the mast cells. These cells are usually distributed in the skin and in the mucosa of gastrointestinal and respiratory tracts, hence the symptoms of itching, flare reactions, bronchoconstriction, nausea and vomiting, diarrhoea and abdominal cramps. Benign skin allergic responses to transfusion of plasma-containing blood components, including RBCs and platelets, manifest as local erythema, urticaria and pruritus in 1–3% of cases. Anaphylactic transfusion reactions are much less frequent (1 in 20 000–400 000 units transfused). In the event of anaphylaxis, the infusion should be stopped immediately and adrenaline administered. Circulatory and respiratory support may be indicated. Diagnosis of an anaphylactic transfusion reaction must be made by demonstrating deficiency of IgA and presence of IgG anti-IgA in the recipient. Patients should subsequently receive blood components from an IgA-deficient donor population or autologous transfusion.

**Recommendation**

*We recommend that multiparous women be excluded from donating blood for the preparation of FFP and for the suspension of platelets in order to reduce the incidence of TRALI. 1C*

Transfusion-related acute lung injury (TRALI) is potentially life-threatening and occurs within 6 h of transfusion of plasma containing blood products. Patients with TRALI commonly present with fever, chills, hypotension, dyspnoea, non-productive cough and cyanosis. Severe hypoxaemia is common, so many patients need supplemental oxygen and mechanical ventilation. Because there is no pathognomonic feature or diagnostic test available for TRALI, diagnosis is by exclusion. Most cases improve within 2–3 days if adequate respiratory and circulatory support is provided. The fatality rate from TRALI is 5–8%. The 2009 SHOT report includes 21 cases of TRALI out of the total of 1279 reported adverse incidents. However, mild forms of TRALI may go unnoticed and severe cases may be attributed to factors such as circulatory overload; therefore, the true incidence is probably underestimated.

In the UK and Belgium, donations from multiparous women are excluded for the preparation of FFP and platelets. This strategy appears to be beneficial in reducing the incidence of TRALI.

In France, HLA antibody screening of previously pregnant female donors has been found acceptable in case of shortage.

**Recommendation**

*We recommend that all RBC, platelet and granulocyte donations from first- or second-degree relatives be irradiated even if the recipient is immunocompetent, and all RBC, platelet and that granulocyte products be irradiated before transfusing to at-risk patients. 1C*

Transfusion-associated graft-versus-host disease (TA-GVHD) is a potential complication if the transfused blood component contains viable T-lymphocytes and there is disparity in HLA-antigens between donor and recipient. The main risk factors are: congenital immunodeficiency disorders; Hodgkin’s disease; *R. typhooidei* infection and premature birth (neonates); intrauterine transfusion; stem cell transplants; donations from first- or second-degree relatives; HLA-matched cellular products; and recipient-donor pairs from genetically homogeneous populations.

The immune cells of immunocompetent recipients far outnumber donor T-lymphocytes, so the latter are usually eliminated by a host-versus-graft response. However, if functional T-lymphocytes are transfused from a donor who is homozygous for one of the recipient’s haplotypes, the recipient may fail to recognise them as foreign. The donor T-lymphocytes recognise the host as foreign, proliferate and cause TA-GVHD. Because the onset of clinical symptoms is delayed for 8–10 days after transfusion, careful monitoring is warranted. Typical features of TA-GVHD include fever, maculopapular skin rash affecting the palms, diarrhoea and hepatitis. Infection leads to deterioration in health, with death occurring within 1 month in over 90% of cases. The quickest way to diagnose TA-GVHD is by skin biopsy; histological changes including basal cell layer degeneration with vacuolisation, dermal epithelial layer separation and bulla formation are evident. It is useful also to establish the persistence of donor T-lymphocytes in the recipient’s circulation or tissues, using DNA analysis. However, their presence alone does not necessarily indicate TA-GVHD because donor lymphocytes can persist after transfusion. Because concomitant medical conditions may conceal TA-GVHD symptoms, the incidence is underestimated.
There is no effective treatment of TA-GVHD. Prevention is by removing donor lymphocytes or by destroying their proliferative capacity. Leukodepletion to less than $10^6$ white cells per unit does not eliminate the risk. However, since the introduction of universal leukodepletion in the UK, a significant decrease in TA-GVHD cases has been observed and the 2009 SHOT report (UK) does not record any cases.\textsuperscript{320} The mainstay of prevention remains gamma irradiation of cellular blood components to prevent donor leukocyte proliferation.\textsuperscript{345} However, because of the low incidence of TA-GVHD in immunocompetent recipients receiving blood components from unrelated donors, gamma irradiation is not warranted on a routine basis.

**Recommendation**

*We recommend the transfusion of leukocyte reduced RBC components for cardiac surgery patients. 1A*

The concept of transfusion-related immunomodulation (TRIM) explains laboratory immune aberrations perceived after blood transfusion. Initially, TRIM only encompassed the effects of allogeneic transfusion attributable to immunomodulation (e.g. cancer recurrence, postoperative nosocomial infection, virus activation), but recently the potential effects of proinflammatory mechanisms (e.g. multiple organ failure, mortality) were added.\textsuperscript{346}

Increased cancer recurrence after blood transfusion has been shown in *in vitro* studies, animal models and observational studies.\textsuperscript{347} However, a randomised controlled study did not find any difference in colorectal cancer recurrence after 2 and 5 years.\textsuperscript{348} The true effect of TRIM on cancer recurrence remains to be demonstrated in a sufficiently powered RCT.

The influence of allogeneic blood transfusion on postoperative nosocomial infections has been investigated in several meta-analyses.\textsuperscript{349–352} However, because of differences in surgical patients, definitions for postoperative infection and type of transfused blood components, the evidence is inconclusive.

Higher mortality rates among transfused versus non-transfused patients can generally be explained by patient selection, because anaemia is an independent risk factor. However, in cardiac surgery, increased postoperative infection attributable to TRIM has been demonstrated among patients receiving leukocyte containing RBCs compared with those receiving leukocyte reduced RBCs.\textsuperscript{353} In the same RCT, inhospital mortality and length of hospital stay were also increased in patients receiving leukocyte containing RBCs. A subsequent RCT conducted by the same authors confirmed the results of their first trial.\textsuperscript{354}

**6.3.3 Preparation of labile blood components**

Because very few indications remain for whole blood transfusion, it is now common for plasma, platelets, RBCs, granulocytes and stem cells to be collected by apheresis. For this technique, one (or more) component(s) are collected from the donor by centrifugation and the unwanted components are returned to the donor’s circulation. The main advantage of apheresis is the collection of more than one dose of a selected component per donation, reducing the number of donors to whom recipients are exposed.

For preparation of FFP at the Belgian Military Hospital, the plasma units are weighed and then subjected to inline leukodepletion by gravity filtration. Pathogen inactivation is performed using the Intercept Blood System (amotosalen and ultraviolet light). Each unit (approximately 200 ml) is frozen at $-75^\circ$C, before storage at $-85^\circ$C for up to 1 year. All FFP units undergo quality control, including determination of factor VIII (FVIII) and protein concentrations, as well as leukocyte, RBC and platelet counts.

Leukodepletion of platelet components takes place during the last step of separation. After a 2 h collection period, aliquots of plasma and suspension liquid are added to produce two platelet units, each containing approximately $4 \times 10^{13}$ platelets. Each platelet unit undergoes pathogen inactivation by amotosalen and ultraviolet light.\textsuperscript{325} Amotosalen is removed by filtration before storage at 20–22°C (shelf life: 5–7 days). Quality control involves measuring volume and pH, as well as platelet, RBC and leukocyte counts. Other techniques used for platelet production are the 'buffy coat' method favoured in Europe and the platelet-rich plasma (PRP) technique used in North America.\textsuperscript{355}

After their separation from whole blood, RBCs are suspended in Nutricel additive solution (Bayer AG, Leverkusen, Germany). Nutricel provides a shelf life of 49 days, 7 days longer than the more commonly used SAGM solution. Promptly after collection, the units are leukodepleted by gravity filtration. Quality control, performed on 1 in 20 units, includes determination of blood group, haemoglobin concentration and haematocrit, leukocyte count, lactate dehydrogenase (LDH), 2,3-diphosphoglycerate (2,3-DPG), adenosine triphosphate (ATP), potassium and lactate concentrations, and pH. European guidelines suggest RBC units produced by apheresis should have a haematocrit of 50–70% when suspended in SAGM solution and 55–70% when Nutricel is used.

**6.3.4 Cell salvage**

**Recommendation**

*We recommend the routine use of red cell saving which is helpful for blood conservation in cardiac operations using CPB. 1A*

In light of the potential adverse effects of transfusing allogeneic blood components, the ever increasing cost and the shrinking donor pool, strategies to reduce perioperative blood transfusion are being developed. Intraoperative cell salvage (ICS) has been proposed as a
key method for reducing perioperative blood transfusion.\textsuperscript{356}

In order to be cost-effective, an initial ‘stand-by’ setup using only a sterile reservoir, a double lumen suction catheter and a solution for anticoagulation is required. Once sufficient wound blood has accumulated, the main washing device is installed. Several devices are available and all use the principle of centrifugation to separate RBCs from plasma and the wash solution. After priming the system with 100–200 ml of heparin solution (30 IU ml\textsuperscript{-1}), the flow is adjusted to an anticoagulant:blood ratio of 1:5 to 1:7.\textsuperscript{357} Shed blood is aspirated, anticoagulated at the suction catheter tip and stored in a sterile reservoir equipped with a microaggregate filter. Anticoagulated and filtered wound blood is pumped into the centrifuge for RBC separation. The RBCs are then washed and suspended in saline to obtain a haematocrit of 50–70%.

Leukocytes are removed with the buffy coat to varying degrees.\textsuperscript{358–361} ICS should be considered for all operations with significant likely blood loss, i.e. >20% of the patient’s estimated blood volume.\textsuperscript{362} Cardiac surgery using CPB is a major indication.\textsuperscript{363} In this setting, significantly reduced blood loss and transfusion requirements have been demonstrated, with decreased complication rates and reduced systemic inflammation related to removal of most but not all cytokines from suctioned blood. Routine use of red cell saving is recommended by the American Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists for blood conservation in cardiac operations using CPB.\textsuperscript{364} However, ICS is contraindicated in patients with infection or malignancy and in situations in which the blood is exposed to topical clothing agents (e.g. fibrin glue or any other thrombin containing compound).

**Recommendation**

*We recommend against the routine use of intraoperative platelet-rich plasmapheresis for blood conservation during cardiac operations using CPB.*

Platelet dysfunction is a major factor in CPB-induced coagulopathic bleeding. It would therefore seem reasonable to remove platelet-rich plasma from circulating whole blood before starting CPB, for infusion at the end of surgery. However, a meta-analysis found that intraoperative platelet-rich plasmapheresis was not beneficial.\textsuperscript{365} The process is labour intensive and technical mistakes might be harmful.\textsuperscript{366}

**6.3.4.1 Other surgical settings**

**Recommendation**

*We recommend the use of red cell salvage in major orthopaedic surgery because it is useful in reducing exposure to allogenic red blood cell transfusion.*

In off-pump cardiac surgery, red cell salvage is recommended. Another area in which ICS has proved to be beneficial is in major orthopaedic surgery, such as hip replacement, spinal operations and repair of pelvic fractures.\textsuperscript{357,367,368} Other indications for ICS include abdominal aortic aneurysm repair,\textsuperscript{369} heptectomy, radical prostatectomy, nephrectomy, cystectomy and emergency medicine (e.g. major abdominal and/or thoracic trauma).\textsuperscript{370}

Definite contraindications to ICS include the intraoperative use of sterile water, hydrogen peroxide or alcohol, as these substances would induce severe RBC haemolysis.\textsuperscript{371} When shed blood is potentially contaminated with bacteria, amniotic fluid or malignant cells, the decision to use ICS should be made on a case-by-case basis.\textsuperscript{356}

In cancer surgery, there is concern about the risk of re-infusing malignant cells, which could cause metastases. Certainly, aspiration of blood from close to the tumour site should be avoided. Leukodepletion may reduce the risk, but residual cancer cells after filtration are unacceptable because it has been demonstrated that one single tumour cell is capable of causing metastasis.\textsuperscript{372} Despite these considerations, studies in urological cancer surgery have shown ICS not to affect biochemical recurrence or long term survival.\textsuperscript{373,374} In 2008, the UK National Institute of Health and Clinical Excellence (NICE) approved the use of ICS in urological malignancy surgery.\textsuperscript{375} It is well known that DNA proliferation of radiosensitive tumour cells can be eradicated by gamma irradiation.\textsuperscript{376,377} Irradiation has also been shown not to impair RBC quality.\textsuperscript{376} Therefore, irradiation of intraoperatively salvaged wound blood could potentially increase the acceptance of ICS in cancer surgery.

**Recommendation**

*We recommend that intraoperative cell salvage is not contraindicated in bowel surgery, provided that initial evacuation of soiled abdominal contents and additional cell washing are performed, and that broad-spectrum antibiotics are used.*

Contamination of the surgical field (e.g. bowel surgery, penetrating abdominal trauma or infected wounds) has typically been considered as a contraindication to ICS. However, the literature indicates no difference in infection rate after laparotomy for abdominal trauma in patients receiving allogeneic blood components or cell salvaged blood. There also seems to be no correlation between microbial organisms grown from cell salvaged blood and those involved in postoperative pneumonia, bacteraemias or urinary tract infections. An RCT in patients undergoing laparotomy for abdominal injuries demonstrated that ICS significantly reduced allogeneic blood usage without increasing postoperative infection or mortality rate.\textsuperscript{378} Consequently, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines state that, in the setting of bowel surgery, red cell salvage is indicated, provided that initial evacuation of the soiled abdominal contents and additional cell...
Leukodepletion filters are advocated because during storage of RBCs, lactic acid accumulates in the blood bag and degrades 2,3-DPG.\textsuperscript{382} This increases the oxygen affinity of haemoglobin, meaning that less oxygen is delivered to tissues. After storage of RBCs for 42 days, the majority of 2,3-DPG is degraded. Although half of it recovers in vivo within 24 h after transfusion,\textsuperscript{383} this might not be fast enough for critical patients needing immediate restoration of oxygen delivery.\textsuperscript{384} In addition, ATP content is reduced in stored RBCs, resulting in morphological changes\textsuperscript{385} which cause changes in blood viscosity. Membrane remodelling may lead to IgG binding and accelerated erythrocyte destruction.\textsuperscript{386} A recent review by Kim-Shapiro\textsuperscript{387} hypothesises that storage-associated RBC fragility causes the release of free haemoglobin, which consumes nitric oxide, a key player in blood flow regulation and inflammation.

Several prospective and retrospective studies have attempted to link prolonged storage duration of RBCs with adverse clinical outcome,\textsuperscript{388–391} but the results are inconclusive. A recent meta-analysis found a lack of support for the suspicion that transfusion of ‘old’ RBCs increases morbidity and mortality.\textsuperscript{392}

Alfano and Tarasev\textsuperscript{393} reported that erythrocyte membrane fragility correlated well with transfusion efficacy and that mechanical fragility differed between RBCs of the same age. These findings suggest that the traditional blood service inventory management founded on the first-in, first-out method could be replaced by an approach taking into account the quality of the RBCs. It would also become possible to prioritise the best performing RBC units for the sickest patients. Recently, Raval et al.\textsuperscript{394} demonstrated that mechanical fragility is independent of age but correlates with storage solution and donor gender. Vincent et al.\textsuperscript{395} suggest that RBC units which may be ineffective for some patients could nonetheless be beneficial for others.

## 7 COAGULATION MANAGEMENT

### 7.1 Indications, contraindications, complications and doses

#### 7.1.1 Introduction

Many treatment protocols for perioperative bleeding use fixed ratios of allogeneic blood products. However, transfusion of allogeneic blood products increases morbidity and mortality, and fixed ratios might not improve outcomes.\textsuperscript{141,396–408} We searched for evidence on the use of fibrinogen concentrate, cryoprecipitate, factor XIII (FXIII) concentrate, recombinant activated factor VII (rFVIIa), PCC, vitamin K, desmopressin (DDAVP), aprotinin and tranexamic acid in severe perioperative bleeding.

#### 7.1.2 Fibrinogen concentrate

**Recommendation**

We recommend treatment with fibrinogen concentrate if significant bleeding is accompanied by at least suspected low fibrinogen concentrations or function.\textsuperscript{1C}

We recommend that a plasma fibrinogen concentration <1.5–2.0 g l\textsuperscript{−1} or ROTEM/TEG signs of functional fibrinogen deficit should be triggers for fibrinogen substitution.\textsuperscript{1C}

We suggest an initial fibrinogen concentrate dose of 25–50 mg kg\textsuperscript{−1}.\textsuperscript{2C}

In severe bleeding, fibrinogen reaches critical concentrations early,\textsuperscript{36,409} and haemorrhagic tendency is increased when fibrinogen concentration is <1.5–2.0 g l\textsuperscript{−1}.\textsuperscript{36,85,114,182,409–414}

Studies have consistently shown that fibrinogen can increase clot firmness,\textsuperscript{124,125,415–429} and data on the efficacy of fibrinogen concentrate in acquired fibrinogen deficiency are increasing. In three randomised trials and two prospective cohort studies, fibrinogen concentrate optimised coagulation, reduced perioperative bleeding and significantly reduced transfusion.\textsuperscript{116,117,430,431} Furthermore, in cardiac surgery, first-line therapy with fibrinogen concentrate and PCC based on POC testing has been associated with decreased transfusion requirements, decreased incidence of thromboembolic events and reduced mortality.\textsuperscript{119,120}

#### 7.1.3 Cryoprecipitate

**Recommendation**

We suggest that the indication for cryoprecipitate is lack of available fibrinogen concentrate for the treatment of bleeding and hypofibrinogenemia.\textsuperscript{2C}

In contrast to cryoprecipitate, freeze dried fibrinogen concentrate offers standardised fibrinogen content, faster reconstitution and improved efficacy.\textsuperscript{432,433} In addition,
the risks of pathogen transmission and immune-mediated complications are reduced with fibrinogen concentrate.\textsuperscript{434,435}

### 7.1.4 Factor XIII

**Recommendation**

In cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentrations, it is likely that FXIII activity is critically reduced. In cases of significant FXIII deficiency (i.e. <60\% activity), we suggest that FXIII concentrate (30 IU kg\(^{-1}\)) can be administered. \textsuperscript{2C}

Clinical studies have shown an increased bleeding tendency in surgical patients with FXIII activity <60\%.\textsuperscript{410,413,436--442} However, more data are needed on the effect of FXIII concentrate on bleeding and transfusion requirements.\textsuperscript{418,443--448}

### 7.1.5 Prothrombin complex concentrate

**Recommendation**

We recommend that patients on oral anticoagulant therapy should be given PCC and vitamin K before any other coagulation management steps for severe perioperative bleeding. \textsuperscript{1B}

We suggest that PCC (20--30 IU kg\(^{-1}\)) can also be administered to patients not on oral anticoagulant therapy in the presence of an elevated bleeding tendency and prolonged clotting time. Prolonged INR/PT alone is not an indication for PCC, especially in critically ill patients. \textsuperscript{2C}

PCC is recommended for acute reversal of oral anticoagulation.\textsuperscript{449,450} Some centres also administer PCC in cases of massive bleeding and prolonged clotting times.\textsuperscript{125,398} although it must be acknowledged that for perioperative bleeding, the data are very limited. Animal trials have shown that PCC can reduce blood loss,\textsuperscript{451--456} and two retrospective analyses have shown benefit in patients with bleeding complications.\textsuperscript{457,458} Other animal studies have shown conflicting results.\textsuperscript{459} A mean dose of 30 IU kg\(^{-1}\) increased normalised PT in patients with reduced coagulation activity.\textsuperscript{460}

Animal studies suggest that PCC administration might be associated with an increased risk of thromboembolic complications or DIC.\textsuperscript{423,461} Vitamin K is required for the synthesis of factors II, VII, IX, and X, and proteins C, S and Z. These factors might be decreased in patients on oral anticoagulant therapy, those with severe malnutrition or severe liver disease, or in newborns. PCC should be administered in these cases of acute severe surgical bleeding.\textsuperscript{119,120,449,450}

### 7.1.6 Recombinant activated factor VII

**Recommendation**

We suggest that off-label administration of rFVIIa can be considered for bleeding which cannot be stopped by conventional, surgical or interventional radiological means and/or when comprehensive coagulation therapy fails. \textsuperscript{2C}

Recombinant FVIIa is licensed for the treatment of patients with haemophilia and inhibitory antibodies, or Glanzmann thrombasthenia.\textsuperscript{462} There is conflicting evidence about the use of rFVIIa in surgical bleeding; reduced blood loss and transfusion requirements have been reported,\textsuperscript{463--466} while some randomised clinical trials have failed to show a benefit. A recent meta-analysis of patients undergoing liver surgery did not find any benefit from prophylactic rFVIIa.\textsuperscript{467} A Cochrane analysis concluded that prophylactic rFVIIa reduced blood loss and transfusion requirements in non-haemophilic patients, while mortality did not change. However, there was also a trend towards increased thromboembolic complications with rFVIIa.\textsuperscript{468,469}

Recombinant FVIIa should be administered before haemostasis is severely compromised.\textsuperscript{470} The optimum dose is 90--120 \(\mu\)g kg\(^{-1}\), and this can be repeated. Hypofibrinogenenaemia,\textsuperscript{471} thrombocytopenia, hypothermia, acidosis and hyperfibrinolysis\textsuperscript{475,476} should all be treated before rFVIIa is used.

### 7.1.7 Antifibrinolytics and tranexamic acid

**Recommendation**

We recommend the consideration of tranexamic acid (20--25 mg kg\(^{-1}\)). \textsuperscript{1A}

The efficacy of antifibrinolytics has been well studied in patients undergoing elective surgical procedures.\textsuperscript{473--477} A large meta-analysis found that tranexamic acid provides a similar reduction in perioperative transfusion to that seen with aprotinin, but with improved safety.\textsuperscript{478--480} Tranexamic acid doses of up to 25 mg kg\(^{-1}\) are usually recommended; these can be repeated or followed by continuous infusion (1--2 mg kg\(^{-1}\) h\(^{-1}\)).

An analysis of tranexamic acid use in 20 211 trauma patients showed that it improves survival rates by approximately 10\%.\textsuperscript{481}

### 7.1.8 Aprotinin

Aprotinin is no longer available. Aprotinin was withdrawn from the market because of safety concerns.

### 7.1.9 Desmopressin (DDAVP)

**Recommendation**

We suggest the use of DDAVP under specific conditions (acquired von Willebrand syndrome). There is no convincing evidence that DDAVP minimises perioperative bleeding or perioperative allogeneic blood transfusion in patients without a congenital bleeding disorder. \textsuperscript{2B}

A Cochrane analysis showed that desmopressin does not significantly reduce the risk of exposure to allogeneic RBC transfusion. In patients undergoing liver resection,
desmopressin has no effect on transfusion requirement.\textsuperscript{482,483} 

In cardiovascular surgery, desmopressin has been shown to reduce postoperative blood loss in patients with severe aortic valve stenosis undergoing aortic valve replacement.\textsuperscript{183} In contrast, desmopressin was not effective in patients undergoing CABG who were previously treated with aspirin.\textsuperscript{484,485}

### 7.2 Correction of confounding factors

#### 7.2.1 Correction of temperature, pH, Ca\textsuperscript{2+}

##### 7.2.1.1 Introduction

Hypothermia and acidosis each induce coagulopathy. A core temperature of \( \leq 34^\circ C \) inhibits thrombin generation, fibrinogen synthesis and platelet function, and increases fibrinolysis. Acidosis (pH \( \leq 7.1 \)) inhibits thrombin generation and platelet function, while accelerating fibrinogen degradation. Reversal of acidosis does not correct acidosis-induced coagulopathy. The positively charged Ca\textsuperscript{2+} enhances fibrin polymerisation, coagulation factor activity and platelet activity.

**Recommendation**

We recommend maintaining perioperative normothermia because it reduces blood loss and transfusion requirements. \textsuperscript{1B}

A meta-analysis found that even mild hypothermia (\(<1^\circ C \) below normal) increases blood loss by approximately 16\% and relative risk of transfusion by approximately 22\% in surgical patients.\textsuperscript{486} Intraoperative maintenance of normothermia has been shown in plastic surgery to support normal coagulation.\textsuperscript{487} In hip arthroplasty, aggressive intraoperative warming (tymanic membrane maintained at 36.5\(^\circ C \)) reduces perioperative blood loss compared with conventional warming (36\(^\circ C \)).\textsuperscript{488} However, in healthy, anaesthetised adults, reduction of body temperature to 32\(^\circ C \) induced only minor effects on coagulation.\textsuperscript{489} Hypothermic effects may go undetected, because coagulation tests are typically performed at 37\(^\circ C \).

A pig model has shown that hypothermia (32\(^\circ C \)) delays onset of thrombin generation (FVIIa/TF pathway) without affecting late thrombin generation (propagation phase). In this study, acidosis (pH 7.1) slightly inhibited early thrombin generation and significantly impaired late thrombin generation.\textsuperscript{490}

**Recommendation**

We suggest that rFVIIa may be used in treatment of patients with hypothermic coagulopathy. \textsuperscript{2C}

While pH correction alone cannot immediately correct acidosis-induced coagulopathy, we recommend that pH correction should be pursued during treatment of acidotic coagulopathy. \textsuperscript{1C}

We recommend that rFVIIa should only be considered alongside pH correction. \textsuperscript{1C}

A pH decrease from 7.4 to 7.0 can reduce FVII activity \textit{in} \textit{vivo} by >90\% and FVII/TF activity by >60\%.\textsuperscript{491} Other \textit{in} \textit{vivo} data show rFVIIa sensitivity to temperature as well as pH.\textsuperscript{492} Addition of rFVIIa \textit{in} \textit{vivo} improves clot reaction times and clot formation rates in mild—moderate, but not severe, hypothermia.\textsuperscript{493} In adult surgical patients, rFVIIa may be less effective in acidic coagulopathy.\textsuperscript{494}

Conversely, rFVIIa efficacy was reported in another study to be affected by volume expansion but not acidosis or hypothermia.\textsuperscript{495}

In thromboelastometric studies of healthy volunteers, hypothermia-induced coagulopathy was exacerbated by acidosis, whereas acidosis without hypothermia had no significant effects on coagulation. Thromboelastometry performed at 37\(^\circ C \) may therefore overestimate the integrity of coagulation for patients experiencing hypothermia and acidosis.\textsuperscript{496}

A study in pigs showed that acidosis-induced depletion of plasma fibrinogen concentration and platelet count is not reversed by neutralisation of pH with bicarbonate.\textsuperscript{497}

**Recommendation**

We suggest that calcium should be administered during massive transfusion if Ca\textsuperscript{2+} concentration is low, in order to preserve normocalcaemia (\( \geq 0.9 \text{ mmol} l^{-1} \)). \textsuperscript{2B}

In a cohort study, the nadir of Ca\textsuperscript{2+} concentration was more important than the lowest recorded fibrinogen concentration, acidosis and platelet count in predicting hospital mortality. Major risk factors for severe hypocalcaemia included acidosis and amount of FFP transfused.\textsuperscript{498} Whole blood clotting time is prolonged in rats with severe ionised hypocalcaemia.\textsuperscript{499}

FVIIa activity is calcium dependent. Thus, Ca\textsuperscript{2+} may stimulate intrinsic FVIIa activity by a combination of charge neutralisation and loop stabilisation.\textsuperscript{500}

#### 7.2.2 Emergency radiological/surgical interventions to reduce blood loss

##### 7.2.2.1 Introduction

Angiotherapy can be diagnostically and therapeutically effective in patients with gastrointestinal bleeding. It provides a surgical alternative for patients with high surgical risk. Candidate patients have typically failed to respond to medical and/or endoscopic therapy.

**Recommendations**

We suggest that endovascular embolisation is a safe alternative to open surgical intervention after failed endoscopic treatment for upper gastrointestinal bleeding. \textsuperscript{2C}

We suggest superselective embolisation as primary therapy for treatment of angiogram positive lower gastrointestinal bleeding. \textsuperscript{2C}

We suggest embolisation as first-line therapy for arterial complications in pancreatitis. \textsuperscript{2C}
Transcatheter arterial embolisation (TAE) is well tolerated and effective for upper gastrointestinal bleeding after failed endoscopic treatment.\textsuperscript{501,502} It has a lower mortality rate than surgery,\textsuperscript{503,504} and low incidences of technique-related complications and recurrent bleeding.\textsuperscript{505,506} When a microcatheter cannot be advanced to the bleeding site, TAE with N-butyl cyanoacrylate may be used to treat upper gastrointestinal bleeding, even in coagulopathic patients.\textsuperscript{507}

TAE can also be used for lower gastrointestinal bleeding,\textsuperscript{508} with a success rate of 76–97% and low frequencies of acute ischaemia or recurrent bleeding.\textsuperscript{509–511} TAE is less invasive than surgery and equally successful in controlling arterial bleeding in pancreatitis.\textsuperscript{512} In patients with head and neck cancer and massive tumour bleeding, TAE has a low incidence of adverse events and is associated with longer survival than that in patients who are not candidates for the procedure.\textsuperscript{513}

7.3 Cost implications

7.3.1 Introduction

Hospital care providers have limited resources and funds allocated for transfusion divert funding from competing clinical and therapeutic strategies. The total cost of supplying patients with haemostatic therapies involves a complex array of activities surrounding the supply process, together with the cost of the consequences following administration. For example, unnecessary transfusions are likely to be associated with unnecessary morbidity and additional indirect hospitalisation costs. In this section, we assess the direct and indirect cost implications of haemostatic therapies.

7.3.2 Do bleeding, massive haemorrhage and transfusion of allogeneic blood products increase costs?

Recommendation

Bleeding and transfusion of allogeneic blood products independently increase morbidity, mortality, length of stay in ICU and hospital, and costs. B

Bleeding and transfusion of allogeneic blood products (e.g. packed RBCs, FFP, platelets) are independently associated with increased morbidity and mortality.\textsuperscript{3,4,321,388,396,399,400,514–519} Thus, allogeneic blood transfusion is associated with increased costs.\textsuperscript{515,520} These costs can be differentiated into primary or acquisition costs for allogeneic blood products (paid by the hospital or the government), activity based costs of blood transfusion (including all process costs from the indication to blood transfusion until monitoring of effects and adverse events) and secondary costs of transfusion-associated adverse events.\textsuperscript{521} Acquisition costs for allogeneic blood products differ widely among countries in Europe and are difficult to determine in countries where hospitals do not have to pay for allogeneic blood products because these are supplied ‘free of charge’ by the government. However, activity based costs are usually 3.2–4.8 times higher than acquisition costs.\textsuperscript{522} Some hospitals use virtual internal transfer prices, which have to be ‘paid’ by the transfusing department to the blood bank in order to compensate for activity based costs of the blood bank (e.g. storage and crossmatching). Furthermore, transfusion-associated adverse events such as acute lung injury (ALI), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), nosocomial infections and sepsis, as well as ischaemic events (myocardial infarction, stroke, acute renal failure, multiple organ failure) are associated with secondary costs for hospitals, governments and health insurance companies. It has been shown that each additional day with mechanical ventilation at a US ICU increases the hospital cost by $3800–4000.\textsuperscript{523,524} In the UK, the ‘return-to-theatre cost’ resulting from a bleeding complication in cardiac surgery has been calculated as £2617.\textsuperscript{525} Furthermore, a study in cardiac surgery in Augsburg, Germany, demonstrated that excessive postoperative haemorrhage, defined as drainage volume >200 ml in any one of the first 6 h after surgery, was associated with significant increases in adverse events (e.g. four-fold increase in the incidence of stroke; incidence of renal failure doubled), length of ICU stay (doubled), mortality (four-fold increase) and hospital costs (increased from £8027 to £15 404).\textsuperscript{526} Murphy et al.\textsuperscript{515} reported that overall hospitalisation costs increased by >40% in transfused compared with non-transfused patients in cardiac surgery in the UK. Therefore, clinical interventions which prevent or address severe perioperative bleeding, reduce transfusion requirements and reduce transfusion-associated adverse events are likely to be cost-effective.

7.3.3 Does prophylactic use of antifibrinolytic drugs or recombinant factor VIIa reduce costs?

Recommendations

Lysine analogues (tranexamic acid and e-aminocaproic acid; EACA) reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several settings of major surgery and trauma. A

We recommend restricting the use of rFVIIa to its licensed indication because, outside these indications, the effectiveness of rFVIIa to reduce transfusion requirements and mortality remains unproven and the risk of arterial thromboembolic events as well as costs are high. 1A

Literature regarding the use of aprotinin to reduce bleeding and transfusion requirements has not been analysed because aprotinin was withdrawn from the market in 2007.\textsuperscript{475,527,528} Lysine analogues (tranexamic acid and EACA) have been shown to reduce the requirement for allogeneic blood transfusion in orthopaedic surgery,\textsuperscript{477,529–538} trauma,\textsuperscript{18,481}
cardiac surgery, postpartum haemorrhage, and liver resection and transplantation.

Head-to-head comparisons show a lower risk of death with lysine analogues compared with aprotinin. The lysine analogues appear to be free of serious adverse effects, but safety data are sparse. Tranexamic acid has been shown to be cost-effective, reducing transfusion requirements without increasing the incidence of deep vein thrombosis. Lysine analogues appear to be particularly cost- and lifesaving in countries with limited financial resources. Cost-effectiveness analysis based on the CRASH-2 trial data indicated that early administration of tranexamic acid to bleeding trauma patients is highly cost-effective in all income settings.

No prospective randomised trials dealing with the prophylactic administration of rFVIIa have shown any effect on mortality. The costs for 400 µg kg⁻¹ rFVIIa are very high compared to a reduction in transfusion requirement of 2.6 U RBCs. Prospective randomised trials in patients with intracerebral haemorrhage showed a significantly increased incidence of arterial thromboembolic complications, including myocardial and cerebral infarction (7 vs. 2% [P = 0.12] and 10 vs. 1% [P = 0.01], respectively). A distinct trend towards serious thromboembolic adverse events, including stroke, was observed in prospective randomised studies in liver transplantation (placebo 10%; 60 µg kg⁻¹ rFVIIa 19%; 120 µg kg⁻¹ rFVIIa 12%; P = 0.05) and cardiac surgery (placebo 7%; 40 µg kg⁻¹ rFVIIa 14% [P = 0.25]; 80 µg kg⁻¹ rFVIIa 12% [P = 0.43]). Most recent guidelines recommend not to use rFVIIa in non-approved indications. Its emergency use should be restricted to situations in which all other options failed to control severe bleeding.

7.3.4 Does cell salvage reduce costs? Recommendation
Cell salvage can be cost-effective. A
Cell salvage has been shown to be cost-effective in minimising perioperative transfusion of allogeneic blood products.

7.3.5 Do formula driven transfusion protocols (1:1:1 concept for RBC:FFP:platelet transfusion) reduce costs? Recommendation
The cost-effectiveness of a formula driven transfusion protocol has not been investigated.

Several retrospective and some prospective cohort studies – mostly performed in military trauma patients – suggest that early fresh frozen plasma transfusion with an FFP to PRBC ratio between 1:2 and 1:1 reduces 30-day mortality. However, the evidence for this is of low quality, with a lack of prospective randomised trials. There are no data on the impact of formula driven transfusion protocols on costs.

7.3.6 Does implementation of point-of-care diagnostics (thromboelastography, thromboelastometry, platelet function tests such as whole-blood impedance aggregometry) and subsequent goal-directed therapy reduce costs? Recommendation
Implementation of transfusion and coagulation management algorithms (based on ROTEM/TEG) can reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation.

O’Keeffe et al. and Cotton et al. demonstrated in two retrospective studies in trauma patients that the implementation of a massive transfusion or exsanguination protocol significantly reduced overall blood product consumption and produced cost savings. Furthermore, Görlinger et al. showed in two retrospective studies in visceral surgery, liver transplantation and cardiovascular surgery that the implementation of a thromboelastometry-based transfusion and coagulation management algorithm significantly reduced transfusion requirements and costs. These results were confirmed by a recent prospective randomised clinical trial in coagulopathic cardiac surgery patients. A significant reduction in transfusion requirements, transfusion-associated adverse events and costs, as well as improved outcomes (including 6-month mortality), was demonstrated in the POC compared to the control group.

In principle, point-of-care tests of haemostatic function can facilitate the optimal management of excessive bleeding and reduce transfusion by enabling tailored haemostatic therapy and differentiation between microvascular and surgical bleeding. The potential reductions in allogeneic blood product transfusion and re-exploration rates have important implications for overall patient safety and healthcare costs. For example, re-exploration for bleeding in patients undergoing coronary artery bypass surgery is associated with a 4.5-fold increase in overall perioperative mortality. Spalding et al. (1422 cardiac surgery patients) and Görlinger et al. (3865 cardiac surgery patients) demonstrated significant reductions in allogeneic blood product transfusion and cumulative costs for allogeneic blood products and coagulation factor concentrates after implementation of thromboelastometry-guided coagulation management algorithms. Similar results, including significant reductions in transfusion and coagulation management costs, were reported by Görlinger et al. and Hanke et al. after implementation of thromboelastometry-guided algorithms in visceral surgery, liver transplantation, and aortic arch replacement in acute type A aortic dissection in a German university hospital.

Further multicentre prospective randomised clinical trials evaluating ROTEM/TEG-guided goal-directed...
therapy (‘theragnostic’ approach) versus fixed ratio concepts (1:1:1 approach) in trauma patients and other clinical settings are urgently needed.

7.3.7 Does goal-directed therapy with coagulation factor concentrates (fibrinogen and/or prothrombin complex concentrate) reduce costs?

Recommendation
Goal-directed therapy with coagulation factor concentrates (fibrinogen and/or PCC) may reduce transfusion-associated costs in trauma, cardiac surgery and liver transplantation. B

Fibrinogen deficiency plays a major role in trauma-induced coagulopathy and other clinical settings associated with severe bleeding. Administration of fibrinogen concentrate has been demonstrated to be consistently effective in animal models and in patients with acquired fibrinogen deficiency. The efficacy, safety and cost-effectiveness of modern four-factor PCCs for rapid reversal of oral anticoagulation has been proven in several cohort and prospective, randomised studies.

There is growing evidence that targeted therapy using coagulation factor concentrates guided by viscoelastic measurements enables effective correction of severe coagulopathy. Görlinger et al. demonstrated in a retrospective study (3865 cardiac surgery patients) that first-line therapy with coagulation factor concentrates (fibrinogen and PCC) based on point-of-care coagulation testing (ROTEM and Multiplate) decreased allogeneic blood transfusion, thrombotic/thromboembolic events and costs, and a more recent study confirmed these results. Similar results, including significant reduction of transfusion and coagulation management related costs, were reported by Görlinger et al. in visceral surgery and liver transplantation. Furthermore, in a study modelling the cost-effectiveness of PCC in emergency warfarin reversal in the United Kingdom, PCC appeared to be more cost-effective than FFP.

7.3.8 Is the use of coagulation factor concentrates (fibrinogen and/or prothrombin complex concentrate) associated with an increased incidence of thromboembolic events and costs?

Recommendation
Thromboembolic events are associated with increased inhospital and post-hospital costs. B

Targeted therapy with fibrinogen and/or PCC guided by ROTEM/TEG is not associated with an increased incidence of thromboembolic events. C

Both bleeding and blood transfusion increase the incidence of ischaemic and thromboembolic adverse events and costs. Here, both bleeding complications and thromboembolic events result in significantly increased costs both inhospital and after discharge. Furthermore, off-label use of rFVIIa, either prophylactically or therapeutically, has been shown to be associated with an increased risk of arterial thromboembolic events. However, Görlinger et al. demonstrated in a large retrospective cohort study (3865 cardiac surgery patients) that first-line therapy with fibrinogen concentrate and PCC based on ROTEM analysis was associated not only with decreased allogeneic blood transfusion but also with a significantly reduced incidence of thrombotic/thromboembolic events (1.77 vs. 3.19%; \( P = 0.0115 \)) and costs. These results were confirmed by a recent study in which the incidence of thromboembolic events was 0% in the PCC versus 4% in the control group. This suggests that secondary costs may be reduced by preventing thromboembolic events due to a targeted haemostatic therapy in bleeding patients. However, this effect has to be confirmed by larger safety studies. Furthermore, a recently published cohort study on the safety and efficacy of PCC and fibrinogen concentrates in 266 patients undergoing liver transplantation did not show a significantly increased incidence of thromboembolic events in patients receiving coagulation factor concentrates compared to patients who did not need any haemostatic intervention (7.1% vs. 4.5%; \( P = 0.31 \)). Details about the risk of thromboembolic events associated with PCC in the setting of VKA reversal are presented in section 7.3 and section 8.3.

8 MULTIMODAL APPROACH (ALGORITHMS) IN SPECIFIC CLINICAL FIELDS

8.1 Cardiovascular surgery

8.1.1 Introduction

Complex cardiovascular surgery may be accompanied by major blood loss, which can lead to loss and consumption of coagulation factors and haemodilution. Coagulopathy in cardiac surgery patients may be exacerbated by concurrent antithrombotic therapy, extracorporeal circulation, hypothermia and volume replacement using crystalloids/colloids. Failure to restore haemostasis and restrict perioperative bleeding increases the risk of re-exploration, transfusion requirements, time spent in the ICU, morbidity and mortality. In this section, we assess the best evidence on the use of different haemostatic therapies to control perioperative bleeding in cardiovascular surgery.

8.1.2 Which therapies influence perioperative bleeding when administered in the preoperative period?

Recommendations
Withdrawal of aspirin therapy increases the risk of thrombosis; continuation of aspirin therapy increases the risk of bleeding. A


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Withdrawal of clopidogrel therapy increases the risk of thrombosis; continuation of clopidogrel therapy increases the risk of bleeding. A

We recommend that a prophylactic dose of low molecular weight heparin should be administered subcutaneously 8–12 h before elective CABG surgery. This intervention does not increase the risk of perioperative bleeding. IB

We recommend that tranexamic acid or EACA should be considered before CABG surgery. IA

We suggest considering prophylactic preoperative infusion of 2 g fibrinogen concentrate, because it may reduce bleeding following elective CABG surgery. 2C

Prothrombin complex concentrate is effective for rapid reversal of oral anticoagulation before cardiac surgery. A

8.1.2.1 Antiplatelet therapies

Aspirin. Aspirin is widely used to treat coronary artery disease. Because aspirin impairs platelet aggregation, discontinuation of aspirin therapy may be considered before elective CABG surgery to minimise perioperative bleeding risk. Management of patients receiving aspirin has been discussed in several guidelines which recommend that aspirin is withdrawn between 2 and 10 days before elective CABG surgery.364,614–616

Urgent or emergency CABG is often performed on patients receiving aspirin up to the day of surgery. A recent meta-analysis of eight RCTs concluded that treatment with ≥325 mg per day of aspirin within 7 days of on-pump CABG surgery increased postoperative mediastinal drainage volume (doses <325 mg did not increase bleeding).617 The authors concluded that a large RCT is needed to assess the effects of preoperative aspirin in the contemporary cardiovascular setting. These data corroborated findings from another meta-analysis (ten studies; five RCTs)618 and a single-blind RCT (n = 200),619 each showing that aspirin intake <7 days before CABG increased postoperative chest-tube drainage volume and RBC and FFP transfusion requirements. Among the studies included in the meta-analysis by Alghamdi et al. was a double-blind RCT demonstrating that the increased blood loss associated with preoperative aspirin was most apparent for patients carrying the GPIIIa allele P1.106 For these patients, additional haemostatic measures such as antifibrinolytic drugs, FFP or platelet transfusions may be considered.106

Clopidogrel. Preoperative clopidogrel therapy may increase postoperative bleeding after CABG. Existing guidelines recommend discontinuing clopidogrel 5–7 days before elective surgery.614–616,620 A meta-analysis of 11 comparative studies (4002 patients) concluded that clopidogrel administration within 5–7 days before urgent CABG surgery increases blood loss and transfusion requirements for RBC, FFP and platelets.621 These findings were supported by a later systematic review (23 studies) reporting that clopidogrel exposure within 7 days before CABG could increase major bleeding, haemorrhagic complications and transfusion requirements.622 In elective CABG, a three-arm RCT (n = 130) subsequently compared clopidogrel therapy continued up to surgery with clopidogrel discontinuation at 3 or 5 days preoperatively.623 Continued clopidogrel therapy resulted in increased blood loss at 12 h and at drain removal, plus increased postoperative homologous blood and FFP transfusion. Outcomes did not differ significantly between clopidogrel discontinuation at 3 vs. 5 days.

8.1.2.2 Heparin

Heparins may be administered before CABG to reduce the risk of deep vein thrombosis, particularly following discontinuation of antiplatelet therapy. In a prospective study (n = 75) comparing preoperative aspirin, subcutaneous unfractionated heparin (UFH) and a no-treatment control, preoperative UFH therapy caused the greatest reduction of postoperative chest-tube drainage volume following CABG surgery.624 Recent guidelines from the American College of Cardiology Foundation and the American Heart Association625 recommend that the use of UFH can be continued until a few hours before CABG and that low molecular weight heparin (LMWH) can be administered ≤12 h before surgery, each without increased perioperative blood loss. Prospective comparison (n = 64) of subcutaneous LMWH (enoxaparin), intravenous heparin and no-treatment control has shown that enoxaparin does not increase bleeding or transfusion requirements when given >8 h before coronary artery bypass.626 Additionally, a randomised comparison (n = 43) of UFH and enoxaparin showed that subcutaneous administration of each, up to 12 h before surgery, has similar effects on coagulation parameters, whole blood count, and RBC and FFP transfusion requirements following elective CABG surgery.627

8.1.2.3 Warfarin

No studies addressing the effects of preoperative warfarin therapy on perioperative bleeding in cardiovascular surgery were retrieved. Recommendations concerning cessation of warfarin therapy before cardiac surgery have been presented elsewhere.614

8.1.2.4 Antifibrinolytic therapy (tranexamic acid and epsilon-aminocaproic acid)

Numerous studies have reported the use of the antifibrinolytic drugs aprotinin, tranexamic acid and EACA to reduce blood loss in cardiovascular surgery. However, aprotinin was withdrawn worldwide following a multicentre RCT (n = 2331) which demonstrated an increased risk of mortality associated with its use, compared with tranexamic acid and EACA, in high-risk cardiac surgery.473 Recent Italian recommendations for preoperative management of perioperative transfusion report that
Tranexamic acid is favoured over EACA in cardiovascular surgery due to the increased potency of tranexamic acid and the increased availability of supporting evidence.\textsuperscript{57}

Tranexamic acid is typically administered continuously during surgery, although use of a single preoperative bolus has been reported. A best evidence topic presented 12 studies reporting prophylactic use of tranexamic acid in cardiac surgery and concluded that tranexamic acid reduces blood loss, transfusion requirements and reoperation due to bleeding.\textsuperscript{628} Among the doses reported were single boluses in the ranges of 2–10 g and 20–150 mg kg\textsuperscript{−1} before sternotomy. One double-blind placebo-controlled randomised trial (\(n = 80\)) also showed that 30 mg kg\textsuperscript{−1} tranexamic acid given immediately before CPB reduced blood loss up to 16 h after elective CABG in patients receiving aspirin up until surgery.\textsuperscript{539} Consistent with these data, a double-blind placebo-controlled randomised trial (\(n = 100\)) showed that 2 g tranexamic acid administered before incision reduced 4 h postoperative blood loss after off-pump CABG with cell salvage.\textsuperscript{629} This confirmed results from two previous placebo-controlled randomised trials assessing the efficacy of 100 mg kg\textsuperscript{−1} tranexamic acid administered before incision. One double-blind trial (\(n = 312\)) reported tranexamic acid to reduce perioperative blood loss and transfusion rates during CABG with cardiopulmonary bypass (CPB).\textsuperscript{630} The other (\(n = 22\)) demonstrated that tranexamic acid reduced intra- and postoperative blood loss during elective surgery with CPB.\textsuperscript{631}

No prospective studies were identified which compared a single preoperative bolus of tranexamic acid with tranexamic acid administration throughout surgery. However, a four-arm prospective randomised trial (\(n = 150\)) compared a preoperative bolus of EACA with two intraoperative EACA dosing regimens and a no-treatment control in elective CABG.\textsuperscript{632} Although EACA administration reduced postoperative chest-tube drainage volume when administered preoperatively, the effect was significantly enhanced by administering EACA intraoperatively.

\subsection{8.1.2.5 Desmopressin (DDAVP)}

No evidence was identified describing preoperative use of desmopressin in cardiovascular surgery. Existing guidelines on perioperative blood transfusion and blood conservation in cardiac surgery suggest preoperative utility of desmopressin may be limited to a small number of patients diagnosed as having defects in primary haemostasis.\textsuperscript{364}

\subsection{8.1.2.6 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)}

A prospective randomised trial (\(n = 40\)) was identified in which FFP was compared with prothrombin complex concentrate (PCC) for reversal of oral anticoagulation prior to CPB in semi-urgent cardiac surgery.\textsuperscript{633} Patients receiving FFP did not reach target INR values within 15 min and even multiple FFP dosing failed to achieve the target INR in 80% of cases, necessitating administration of PCC. No further studies were identified which evaluated preoperative transfusion with FFP, platelets or cryoprecipitate.

\subsection{8.1.2.7 Coagulation factor replacement therapy}

\textbf{Antithrombin (AT) concentrate.} It has been proposed that AT (previously AT III) may limit consumptive coagulopathy by suppressing thrombin generation during cardiac surgery. This was investigated in a double-blind RCT (\(n = 20\)) in which placebo or AT was infused before incision in elective CABG patients.\textsuperscript{634} No difference in postoperative blood loss at 6 or 12 h was evident between the AT and placebo groups. Recommendations on the use of AT concentrates suggest that further studies are needed in patients undergoing extracorporeal circulation.

\textbf{Fibrinogen concentrate.} A prospective randomised pilot study (\(n = 20\)) demonstrated that prophylactic fibrinogen infusion is potentially useful for reducing bleeding after elective CABG.\textsuperscript{430} Compared with untreated controls, patients receiving 2 g fibrinogen concentrate immediately before surgery experienced reduced 12 h chest-tube drainage volume, with no apparent hypercoagulability.

\textbf{Prothrombin complex concentrate (PCC).} A four-factor PCC has been shown to be more effective than FFP for reversal of oral anticoagulation in semi-urgent cardiac surgery.\textsuperscript{633} Compared with FFP, administration of a half-dose of PCC (based on body weight and initial INR, according to the manufacturer’s instructions) prior to CPB resulted in faster correction of INR, with less associated bleeding.

\textbf{Recombinant activated factor VII (rFVIIa).} rFVIIa has been administered preoperatively ahead of successful palliative open heart surgery in a cyanotic infant with FVII deficiency.\textsuperscript{636} A dose of 30 μg kg\textsuperscript{−1} rFVIIa was administered 2 h before surgery and then another immediately before surgery, with further doses postoperatively. No further reports of preoperative rFVIIa therapy were identified.

\subsection{8.1.3 Which therapies can be used to control bleeding intraoperatively?}

\textbf{Recommendations}

We recommend that intraoperative tranexamic acid or EACA administration should be considered to reduce perioperative bleeding in high-, medium- and low-risk cardiovascular surgery. \textit{IA}

We recommend that tranexamic acid should be applied topically to the chest cavity to reduce postoperative blood loss following CABG surgery. \textit{IC}
We recommend that fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiovascular surgery. 1B

We suggest that recombinant FVIIa may be considered for patients with intractable bleeding during cardiovascular surgery once conventional haemostatic options have been exhausted. 2B

8.1.3.1 Heparin
Heparin anticoagulation is used during cardiovascular surgery to limit coagulation factor activation, thus preventing overt thrombosis of the CPB circuit. Heparin dosing may be partially influenced by the length of time spent on CPB and patient responses to heparin may be variable. Dosing and monitoring of heparin anticoagulation is addressed in guidelines on perioperative blood conservation management in cardiac surgery364 and also on antiplatelet and anticoagulation management in cardiac surgery.614 We retrieved four prospective studies (n = 26, n = 39, n = 44 and n = 53) investigating heparin monitoring using heparin concentration-based approaches, as opposed to a standard activated clotting time-based approach, during cardiac surgery.637–640 Use of heparin concentration-based systems was consistently associated with reduced postoperative blood loss and increased avoidance of transfusion. Although useful in principle, heparin concentration-based monitoring is not widely used in clinical practice. In addition, a number of monitoring devices are available, so large randomised trials comparing different systems may be warranted.

8.1.3.2 Protamine
Administration of protamine is commonly used to reverse the effects of heparin anticoagulation. Correct dosing of protamine is important because insufficient protamine results in residual heparin. Conversely, excess protamine also impairs coagulation, possibly due to antiplatelet activity.641 Protamine dosing in cardiac surgery is addressed in guidelines on the management of perioperative blood conservation364 and also on the management of antiplatelet and anticoagulation therapy.614 The prospective studies that we identified which investigated heparin monitoring using heparin concentration-based approaches all found that heparin concentration-based measurements led to administration of smaller doses of protamine.637–640 If these results are confirmed in larger studies, and if such approaches become part of normal practice, heparin concentration-based monitoring could improve the accuracy of protamine dosing. Another important issue concerning protamine administration in cardiac surgery is uncertainty over acceptable ratios of protamine to heparin. Typical ratios of protamine to heparin are around 1.3:1, although a best evidence topic on the risk of bleeding associated with high-dose protamine reported that increased bleeding and impaired platelet function had not been reported below a protamine to heparin ratio of 2.6:1.643 This contrasts with reports suggesting that lower ratios (1.5:1 in vitro642 and 1.3:1 in vivo644) can prolong coagulation and impair platelet function. Further studies are required to clarify the most appropriate ratios of protamine to heparin for use in cardiac surgery.

8.1.3.3 Antifibrinolytic therapy (tranexamic acid and ε-aminocaproic acid)
Intraoperative antifibrinolytic therapy is covered in guidelines for blood conservation364 and anticoagulation management614 in cardiac surgery. Each recommends using aprotinin, tranexamic acid or EACA to limit blood loss and transfusion requirements. Safety and efficacy outcomes for each drug have been compared in a meta-analysis of 138 RCTs in cardiac surgery.528 Aprotinin, tranexamic acid and EACA all reduced perioperative blood loss and RBC transfusion compared with placebo. High-dose aprotinin showed the greatest efficacy, although aprotinin also increased the risk of renal dysfunction. This finding was consolidated by the BART (blood conservation using antifibrinolytics in a randomised trial) study (n = 2331),475 which compared aprotinin, tranexamic acid and EACA in high-risk cardiac surgery (all administered as a preoperative bolus, followed by continuous intraoperative infusion), and was terminated early due to an elevated mortality rate associated with aprotinin. Aprotinin was subsequently withdrawn from the market and further meta-analyses using RCT data have confirmed the increased mortality risk associated with aprotinin in cardiac patients.545,646

Since aprotinin was withdrawn, it has not been established whether tranexamic acid or EACA is the better therapeutic option. Further analysis of the BART study data found no differences in safety or clinical effectiveness of tranexamic acid and EACA, although lower costs were reported for EACA.647 Data supporting EACA administration was identified from a double-blind, placebo-controlled randomised trial (n = 78) in which EACA was found to be as effective as aprotinin for reducing blood loss during CABG surgery.648 Conversely, a recent three-arm RCT (n = 90) comparing antifibrinolytic drugs in open heart surgery found that both aprotinin and tranexamic acid significantly reduced blood volumes in suction bottles and drainage tubes compared with EACA.649 Tranexamic acid also exhibited the least evidence of renal dysfunction. Although neither tranexamic acid nor EACA has been conclusively demonstrated as being superior in the cardiovascular setting, we identified more high quality evidence published since 2007 which supports use of tranexamic acid than was identified for EACA. This includes a double-blind, placebo-controlled randomised trial (n = 222) showing that tranexamic acid (preoperative bolus followed by infusion throughout CPB) decreased chest-tube drainage volume and
transfusion requirements following elective CABG. Also identified was a double-blind RCT \((n = 220)\) evaluating tranexamic acid versus aprotinin infusion throughout primary CABG or valve replacement surgery, which showed no overall difference in blood loss or RBC transfusion between treatment groups. Similarly, a three-arm RCT \((n = 298)\) comparing aprotinin, tranexamic acid and placebo in low- to medium-risk CPB patients found that tranexamic acid significantly reduced blood loss and transfusion requirements compared with placebo, without increasing the incidence of serious adverse events. Additionally, a meta-analysis of 25 RCTs \((n = 5411)\) and four matched observational studies \((n = 5977)\) was retrieved, which concluded that tranexamic acid has clear benefits in reducing blood loss, reoperation for bleeding and transfusion with allogeneic blood components compared with placebo.

Tranexamic acid administration regimens vary widely. Our evidence base typically reported an initial bolus after induction of anaesthesia, followed by continuous infusion during CPB. Tranexamic acid may also be added to the bypass circuit, or another bolus administered before chest closure. One RCT was identified which directly assessed the benefits of tranexamic acid given intraoperatively; a double-blind trial examined 67 children with cyanotic congenital heart defects undergoing surgery with CPB. All patients received 15 mg kg\(^{-1}\) tranexamic acid before incision, then either placebo or an identical dose of tranexamic acid at the end of CPB. Blood loss and transfusion requirements did not differ between the groups. Tranexamic acid may also be used topically. A double-blind RCT \((n = 38)\) compared topical application of tranexamic acid \((1 \text{ g in } 100 \text{ ml saline})\) or placebo to the pericardial and mediastinal cavities before chest closure following CABG. Tranexamic acid reduced postoperative chest-tube drainage volume and platelet transfusion requirements compared with placebo.

Variation in EACA administration regimens has also been reported. Two RCTs were identified which compared EACA dosing regimens. In the first study, patients \((n = 150)\) were randomised to receive no EACA, one 150 mg kg\(^{-1}\) preoperative bolus, one 150 mg kg\(^{-1}\) preoperative bolus plus 1 g h\(^{-1}\) infusion for 6 h, or three separate 150 mg kg\(^{-1}\) boluses before, during and after CPB. The greatest reduction in blood loss and transfusion requirements was seen in the groups receiving EACA intraoperatively. Neither intraoperative regimen proved superior to the other. In a subsequent study, patients \((n = 90)\) received either placebo, a 150 mg kg\(^{-1}\) EACA bolus followed by a 15 mg kg\(^{-1}\) h\(^{-1}\) infusion of EACA commencing before incision, or a 150 mg kg\(^{-1}\) bolus of EACA followed by a 15 mg kg\(^{-1}\) h\(^{-1}\) infusion of EACA commencing after heparinisation. Both EACA regimens reduced chest-tube drainage volumes but the timing did not affect outcomes, suggesting that EACA administration is unnecessary before heparinisation.

Most of the evidence which we retrieved involved use of CPB (on-pump surgery). Off-pump CABG surgery is associated with less blood loss and transfusion than on-pump CABG. A systematic review of eight RCTs was performed to determine the utility of tranexamic acid in off-pump CABG. Tranexamic acid reduced the risk of allogeneic blood component transfusion, but larger trials were deemed necessary to draw conclusions about blood loss and adverse events. We also identified a meta-analysis (17 trials) supporting the use of antifibrinolytic drugs in CABG patients receiving aspirin throughout the perioperative period. Tranexamic acid and EACA all reduced chest-tube drainage volume and perioperative transfusion requirements without increasing the rate of adverse events.

### 8.1.3.4 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)

Patients undergoing cardiovascular surgery are regularly transfused with FFP and/or platelet concentrate. Some patients may also receive cryoprecipitate, although this has been withdrawn in many countries due to safety concerns. Intraoperative use of FFP, platelets and cryoprecipitate is addressed in a guideline on perioperative blood transfusion and blood conservation in cardiac surgery and also in recent Italian recommendations for intraoperative management of perioperative bleeding.

We retrieved no studies examining the haemostatic efficacy of platelet or cryoprecipitate transfusion on perioperative bleeding in cardiac patients, although three systematic reviews were identified which questioned the efficacy of FFP. One review assessed the effects of prophylactic FFP transfusion at the end of CPB in six RCTs; four were conducted in patients undergoing CABG surgery and two reported cardiac surgery with CPB. It was concluded that routine FFP transfusion following CPB did not reduce subsequent blood loss. These findings are consistent with a recent systematic review of RCTs since 2004 which evaluates the clinical effectiveness of FFP. Twenty-one studies were included and a meta-analysis of the largest subgroup (cardiac surgery) showed no significant reduction in 24-h blood loss following FFP transfusion. In addition, a review of seventy studies (including 21 set in cardiovascular surgery) concluded that FFP transfusion was not clinically effective and may even be detrimental.

### 8.1.3.5 Desmopressin (DDAVP)

Much of the evidence concerning intraoperative use of desmopressin has been considered in an existing guideline on perioperative transfusion and blood conservation in cardiac surgery. Potential use of desmopressin is suggested to be limited to excessively bleeding patients.
with primary haemostasis disorders, such as CPB-induced platelet dysfunction and type 1 VWD. Consistent with this, we retrieved two RCTs reporting that administration of 0.3 μg kg⁻¹ desmopressin at the end of CPB did not reduce perioperative blood loss or transfusion requirements in elective CABG (n = 66) or complex congenital heart surgery (n = 60). Similar findings were reported following desmopressin treatment of 100 CABG patients receiving aspirin until the day before surgery.  

8.1.3.6 Coagulation factor replacement therapy

Factor XIII concentrate. A three-arm, double-blind RCT (n = 75) was identified which investigated FXIII concentrate as haemostatic therapy in coronary surgery with extracorporeal circulation. Following protamine administration, patients received placebo or 1250 or 2500 U of FXIII. No significant differences in postoperative blood loss or transfusions were observed. Subgroup analysis indicated that FXIII therapy may be most effective in patients displaying subnormal FXIII levels following CPB.

Fibrinogen concentrate. Two systematic reviews have suggested fibrinogen concentrate to be potentially useful for treating surgical bleeding. One review included 21 trials investigating efficacy of fibrinogen concentrate; three were prospective studies reporting intraoperative use in cardiovascular surgery. The second review included four reports; two were prospective studies in cardiovascular surgery. Each review concluded that fibrinogen concentrate therapy could improve clot firmness and decrease transfusion requirements, blood loss and postoperative drainage volumes. The evidence was acknowledged to be of insufficient quality, indicating a need for large RCTs.

Since then, data has become available from a randomised, double-blind, placebo-controlled trial (n = 61) which supports intraoperative infusion of fibrinogen concentrate during complex cardiovascular surgery. Patients with diffuse bleeding following CPB were treated with thromboelastometry-guided fibrinogen concentrate as first-line haemostatic therapy, which reduced the need for transfusion with RBC, FFP and platelets. These data corroborated findings from two smaller prospective cohort studies, one in repair of thoracoabdominal aortic aneurysm (n = 18), the other involving aortic valve operation with ascending aorta replacement (n = 15). Similarly, thrombelastography guided fibrinogen concentrate therapy following CPB has been reported to reduce postoperative chest tube drainage volume and FFP transfusion in cyanotic children undergoing cardiac surgery.

Prothrombin complex concentrate. Recommendations on the use of PCC suggest that it may help to control intractable bleeding in major surgery, although there is little evidence so far to support this indication in cardiovascular surgery. Two retrospective reports were identified describing intraoperative PCC administration in cardiac patients. Analysis of five patients undergoing CABG and two patients undergoing valve replacement suggested that PCC could be valuable for controlling bleeding in patients responding poorly to standard blood products. An earlier chart review of cardiothoracic surgical patients (n = 60) indicated that PCC could safely reduce blood product consumption. Larger, prospective evaluations are required.

Recombinant activated factor VII. Although indicated for patients with congenital coagulation factor deficiencies, use of rFVIIa has been frequently reported for unlicensed indications in patients with major bleeding. Guidelines for the use of rFVIIa in massive bleeding and for perioperative blood conservation in cardiac surgery recommend that rFVIIa may promote haemostasis during severe intractable bleeding following CPB. However, due to concerns over potential thromboembolic risks, use of rFVIIa is recommended only if all conventional haemostatic options have been exhausted. Additionally, the patient’s next of kin should be informed that rFVIIa is being used outside of the currently approved indications.

We retrieved reports published subsequent to these guidelines which support existing recommendations for rFVIIa in cardiac surgery. Systematic reviews of rFVIIa in cardiac surgery (one including 35 studies and one including 46 studies), paediatric cardiac surgery (29 studies) and vascular surgery (15 studies) concluded that rFVIIa may reduce severe haemorrhage but that large prospective randomised trials are required to define efficacy, dose and side-effects. Similarly, a systematic analysis of rFVIIa in on-pump cardiac surgery (19 studies) recommended against routine prophylaxis and emphasised that although rFVIIa may be considered as rescue therapy, high quality data supporting this indication is lacking.

8.1.3.7 Fibrin sealant (fibrin glue)

Fibrin sealant consists of fibrinogen, thrombin and other additives and can be applied to wounds to create a fibrin-based clot and promote haemostasis. We retrieved a recent prospective RCT in which 82 senior patients received either fibrin sealant or bone wax injected into the sternal marrow cavity after CABG surgery involving CPB. The fibrin sealant group displayed reduced postoperative chest tube drainage volume, less RBC transfusion requirements and a shorter hospital stay. No differences in adverse outcomes were reported. Blinding was not reported so further trials may be required to confirm these findings.

8.1.4 Which therapies influence bleeding in the postoperative period?

Recommendations

We suggest that antiplatelet therapy with aspirin or clopidogrel may be administered in the early...
postoperative period without increasing the risk of postoperative bleeding. 2C

We suggest that rFVIIa may be considered for patients with intractable bleeding after cardiovascular surgery once conventional haemostatic options have been exhausted. 2B

8.1.4.1 Antiplatelet therapies (aspirin and clopidogrel)
Guidelines on the use of aspirin and other antiplatelet agents during CAGB surgery\(^{616}\) and on antiplatelet and anticoagulation management in cardiac surgery\(^ {614}\) make several recommendations on the postoperative administration of antiplatelet therapies. We retrieved no further high quality evidence evaluating the effects of postoperative antiplatelet therapy on postoperative bleeding. However, a prospective, multicentre, observational trial was identified in which patients (\(n = 5065\)) undergoing CAGB received aspirin therapy in the early postoperative period.\(^ {622}\) Aspirin was associated with numerous clinical benefits and was reported to have no association with increased postoperative bleeding. Another prospective observational trial investigated patients (\(n = 117\)) undergoing elective CAGB (on- and off-pump) who were administered aspirin or aspirin plus clopidogrel in the early postoperative period, according to a predefined protocol.\(^ {625}\) Chest-tube drainage, transfusion frequency, transfusion quantity and risk of reoperation for bleeding were all comparable between the groups, indicating that early postoperative clopidogrel does not increase bleeding risks compared with aspirin alone.

8.1.4.2 Antifibrinolytic therapy (tranexamic acid and \(\alpha\)-aminocaproic acid)
A randomised, double-blind, placebo-controlled study was identified which investigated the effects of continued tranexamic acid dosing in the postoperative period following elective cardiac surgery involving CPB.\(^ {624}\) All patients (\(n = 510\)) received 1g tranexamic acid before incision, a continuous infusion of 400 \(\mu\)g h\(^{-1}\) until the completion of operation, and 500 mg in the CPB prime. Thereafter, patients received an infusion for 12h with placebo, 1 mg kg\(^{-1}\) h\(^{-1}\) tranexamic acid or 2 mg kg\(^{-1}\) h\(^{-1}\) tranexamic acid. Postoperative administration of tranexamic acid had no effect on blood loss or transfusion requirements.

8.1.4.3 Allogeneic blood products (fresh frozen plasma, platelets and cryoprecipitate)
No high quality evidence was identified supporting the efficacy of FFP, platelets or cryoprecipitate administered postoperatively following cardiovascular surgery. Administration of allogeneic blood components has been addressed recently by Italian recommendations for postoperative management of perioperative transfusion.\(^ {675}\)

8.1.4.4 Desmopressin (DDAVP)
No high quality evidence was identified supporting the efficacy of postoperative administration of desmopressin in cardiovascular surgery.

8.1.4.5 Coagulation factor replacement therapy
Recombinant activated factor VII. As described for intraoperative therapy, use of rFVIIa to control intractable bleeding constitutes an unlicensed indication. Due to the potential thromboembolic risks, rFVIIa should therefore be considered only if conventional haemostatic approaches have failed. In this situation, guidelines for the use of rFVIIa in massive bleeding\(^ {562}\) and for perioperative blood conservation in cardiac surgery\(^ {664}\) suggest that rFVIIa may be used for refractory bleeding following CPB. The patient’s next of kin should be informed that rFVIIa is being used off-label.\(^ {562}\)

A best evidence topic was identified addressing the question: is rFVIIa useful for intractable bleeding after cardiac surgery?\(^ {676}\) Of 129 reports identified, 13 were presented as the best evidence. The study concluded that a dose of 60–90 \(\mu\)g kg\(^{-1}\) rFVIIa could be used for patients with intractable bleeding post-cardiac surgery, with a repeated dose after 2–4h. A double-blind RCT (\(n = 172\)) was also identified in which rFVIIa was used to treat patients experiencing intractable bleeding after cardiac surgery.\(^ {559}\) Patients received placebo, 40 \(\mu\)g kg\(^{-1}\) 1 rFVIIa or 80 \(\mu\)g kg\(^{-1}\) rFVIIa, on average 2.8h after admission to the postoperative care unit. Treatment with rFVIIa significantly reduced the incidence of reoperation for bleeding and subsequent transfusion requirements, although both rFVIIa groups exhibited a non-significant trend towards increased serious adverse events. This suggests the need for large RCTs to assess safety of rFVIIa in this setting.

8.1.5 What is the evidence for the use of haemostatic management algorithms in cardiovascular surgery? Recommendations
We recommend the use of standardised haemostatic algorithms with predefined intervention triggers. 1A

Several studies have demonstrated that standardised transfusion algorithms for administration of haemostatic therapy can result in reduced perioperative blood loss and transfusion requirements. A recent review evaluated eight studies (five prospective) using preset therapeutic transfusion triggers, measured using laboratory-based haemostasis tests and/or point-of-care coagulation monitoring devices, to guide haemostatic intervention during cardiovascular surgery. In seven of the eight studies, the use of an algorithm significantly reduced patient exposure to allogeneic blood products.\(^ {144}\)

We retrieved additional prospective studies which evaluated the effectiveness of standardised treatment algorithms in cardiovascular surgery. One RCT compared...
cardiac surgery patients ($n = 69$) in whom perioperative transfusion management was conducted in accordance with either a strict TEG-guided protocol (using kaolin-activated TEG and PlateletMapping assays), or physician-directed administration with reference to aPTT, INR, fibrinogen concentration and platelet count. $^{677}$ TEG-based management reduced total blood product usage by almost 60% compared with the laboratory test-based approach, although this was not statistically significant. A larger RCT confirmed the potential value of TEG in guiding haemostatic management. $^{121}$ In this study, patients ($n = 224$) undergoing elective CABG with CPB again received transfusions based on either kaolin-activated TEG or clinicians’ judgement combined with laboratory test results. Patients in the TEG group received significantly lower amounts of FFP, platelets and tranexamic acid, while the total number of units transfused was also lower compared with patients managed using laboratory tests and clinical judgement. Another RCT was identified which supports the use of viscoelastic point-of-care tests to guide coagulation management. $^{125}$ Patients ($n = 56$) requiring aortic surgery with hypothermic circulatory arrest were administered haemostatic interventions according to a ROTEM-guided transfusion algorithm (INTEM, HEPTEM, FIBTEM and APTEM tests) or based on ‘standard practice’ (transfusion guided by clinical judgement and laboratory test results). Postoperative blood loss and rate of reoperation for bleeding were comparable between groups, although ROTEM-guided therapy substantially reduced allogeneic transfusion requirements, particularly for FFP. Furthermore, recent studies have demonstrated that first-line therapy with coagulation factor concentrates (fibrinogen and PCC) based on point-of-care coagulation testing (ROTEM and Multiplate) decreases allogeneic blood transfusion, thrombotic/thromboembolic events and costs. $^{119,120}$

8.2 Gynaecology and obstetrics

8.2.1 Gynaecological (non-pregnant) bleeding

8.2.1.1 Treatment of perioperative anaemia

Gynaecological operations such as cancer surgery and hysterectomy may be complicated by anaemia and perioperative blood loss. $^{678}$ Among gynaecological operations, excision of a malignant ovarian tumour is the most common cause of severe bleeding, $^{679}$ and transfusion and reoperation due to bleeding are prevalent in hysterectomy. $^{680,681}$

Minimising gynaecological RBC transfusion

Recommendation

We suggest against normovolaemic haemodilution because it does not reduce allogeneic transfusion. 2A

Gynaecological oncologists report a mean prechemotherapy transfusion threshold of 7.9 g dl$^{-1}$ haemoglobin (higher for ovarian debulking; lower for endometriosis). $^{682}$ No evidence was identified comparing gynaecological RBC transfusion triggers with those in other settings.

Autologous transfusion $^{683–692}$ and intraoperative haemodilution $^{693–695}$ exemplify strategies to minimise allogeneic transfusion. $^{596}$ However, autotransfusion is associated with high costs, together with risks of laboratory and clerical errors. $^{696–698}$ In addition, transfusion of colloids can result in haemodilution, which may compromise coagulation $^{613,631}$ and therefore may not reduce allogeneic transfusions. $^{699,700}$

Should cell salvage be used in gynaecological surgery?

Recommendation

Cell salvage may reduce allogeneic transfusion in gynaecological (including oncological) surgery. C

Increasing evidence supports the use of filters to clear shed blood of cancer cells, avoiding reinfusion and dissemination. $^{701}$ Retrospective studies suggest that cell salvage reduces allogeneic transfusion requirements. $^{702–706}$

Should intravenous iron or erythropoietin be used to correct perioperative anaemia?

Recommendations

We suggest using preoperative intravenous iron to reduce allogeneic transfusion requirements in gynaecological cancer patients receiving chemotherapy. 2B

We suggest using intravenous iron to correct perioperative anaemia in women with menorrhagia. 2B

Intravenous iron increases haemoglobin concentration and reduces RBC transfusion in anaemic gynaecological cancer patients receiving chemotherapy. $^{707,708}$ without compromising quality of life. $^{708}$ Intravenous iron corrects preoperative anaemia in patients with menorrhagia. $^{213}$ Preoperative erythropoietin increases haemoglobin concentration, particularly if co-administered with iron, $^{235,250,707,709,710}$ but concerns exist regarding safety in cancer patients. $^{678}$

8.2.1.2 Coagulation monitoring and treatment

Gynaecological cancer patients are prone to increased blood viscosity and fibrinogen concentrations, $^{711–713}$ and perioperative transfusion $>2$ l increases the risk of postoperative venous thromboembolism. $^{713}$ Perioperative haemostatic monitoring and intervention is critical.

Use of standard laboratory tests and point-of-care devices for gynaecological coagulation monitoring

Recommendation

Preoperative fibrinogen and D-dimer evaluation in gynaecological cancer patients provide little useful information. C


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Elevated preoperative plasma fibrinogen concentrations and positive D-dimer tests provide little clinically useful information. PT, aPTT and INR may be elevated for several days postoperatively.

**What are the indications for fresh frozen plasma, platelets and fibrinogen replacement therapy?**

**Recommendation**

Postoperative FFP transfusion is associated with an increased risk of venous thromboembolism in malignant gynaecological surgery.

FFP transfusion after surgical exploration for resection of adnexal/peritoneal cancer appears to increase risk of venous thromboembolism without affecting survival, although the study was prone to confounding-by-indication bias. No relevant studies were identified for fibrinogen concentrate or cryoprecipitate in gynaecological surgery.

**What are the indications for recombinant activated factor VIIa?**

**Recommendation**

rFVIIa increases thromboembolic risk and has not been shown to reduce mortality.

rFVIIa has been successfully administered for perioperative bleeding in malignant and non-malignant gynaecological surgery. However, rFVIIa increases the risk of venous thromboembolism, without improving mortality.

No studies examining the use of PCC or FXIII were identified.

**What are the indications for antifibrinolytics (tranexamic acid)?**

**Recommendations**

Tranexamic acid reduces the frequency of late bleeding after cone biopsy of the cervix.

Tranexamic acid reduces perioperative bleeding in gynaecological cancer surgery.

We suggest against the use of tranexamic acid in benign gynaecological operations such as myomectomy.

Tranexamic acid reduces menstrual bleeding in menorrhagia without increased thrombotic risk. Tranexamic acid also protects against late bleeding after cone biopsy of the cervix and reduces blood loss in gynaecological cancer surgery, but not during myomectomy.

**8.2.2 Obstetric bleeding**

**8.2.2.1 Treatment of postpartum anaemia**

Anaemia develops in up to 29% of third trimester pregnancies, while postpartum bleeding is the major risk factor for severe postpartum anaemia. Transfusion in this setting may complicate delivery. Here, we assess whether treating obstetric haemorrhage requires correction of anaemia, and the therapeutic options available.

Related topics of PPH such as diagnosis of PPH, treatment of atony and retained placental tissue, arterial embolisation, etc. is beyond the scope of this guideline. We recommend other evidence-based clinical guidelines such as the WHO guidelines for the management of postpartum haemorrhage and retained placenta.

**Obstetric triggers for red blood cell transfusion**

**Recommendations**

We recommend that peripartum haemorrhage should be managed by a multidisciplinary team. An escalating management protocol including uterotonic drugs, surgical and/or endovascular interventions, and procoagulant drugs should be available.

Risk awareness and early recognition of severe haemorrhage are essential.

We suggest that patients with known placenta accreta are treated by multidisciplinary care teams.

Postpartum haemorrhage (PPH) should be treated promptly. Delayed recognition of and response to acute bleeding is a leading cause of maternal mortality and ‘near misses’. Suboptimal haemotocrit during the acute phase of PPH is associated with end organ dysfunction. In postpartum haemorrhagic shock, myocardial ischaemia is typically associated with impaired contractility at systolic blood pressure <88 mmHg, diastolic blood pressure <50 mmHg and heart rate >115 beats per min.

No clinical studies of transfusion triggers in life-threatening obstetric haemorrhage were retrieved; however, general adherence to a haemoglobin threshold of 8.1 g dl⁻¹ has been reported.

There is currently debate over RBC transfusion triggers for postoperative anaemia. Up to 68% of postpartum transfusions may not adhere to guideline recommendations, and RBC units are often transfused in duplicate without an obvious rationale. Transfusion of 1–2 U of RBCs during postpartum recovery may not impact on length of hospital stay.

Anaemia peaks at around 48h after delivery but may initially go undetected. Haemoglobin concentration and health related quality of life physical fatigue scores correlate in the first week postpartum.

Early diagnosis and treatment of coagulopathic amniotic fluid embolism is associated with increased survival. Treatment by a multidisciplinary team may reduce early maternal morbidity in women with placenta accreta, compared with standard obstetric care.

**Should cell salvage be used in obstetrics?**

**Recommendations**

Cell salvage is well tolerated in obstetric settings, provided that precautions are taken against rhesus isoimmunisation.

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We suggest that using perioperative cell salvage during caesarean section may decrease postoperative homologous transfusion and reduce hospital stay. 2B

Perioperative cell salvage has been used in obstetric surgery but is not widely established due to staff training and technology issues. 243 Concerns exist regarding potential amniotic fluid embolism and rhesus isoimmunisation. 244 Filters reduce contamination with amniotic fluid, 245–247 although fetal RBC may remain after leukocyte filtration, therefore, Kleihauer testing and Anti-D treatment may be recommended. 248 Severe hypertension is rare following infusion of salvaged blood. 250

Cell salvage may be useful for caesarean section, especially for Jehovah’s Witnesses and when complicated by placenta praevia, placenta accreta or reoperation due to bleeding. 244,760–765 Jehovah’s Witnesses who are prepared to accept perioperative cell salvage often require that the system be set up to allow for continuous connectivity, including during transport to the postoperative ward. A comparison with standard treatment has shown cell salvage to reduce postoperative homologous transfusion and hospitalisation. 256

Intravenous iron or erythropoietin in the treatment of postpartum anaemia

Recommendations

We recommend that moderate (<9.5 g dl⁻¹) to severe (<8.5 g dl⁻¹) postpartum anaemia be treated with intravenous iron rather than oral therapy. 1B

Intravenous iron supplementation improves fatigue at 4, 8 and 12 weeks postpartum. B

Insufficient evidence exists to support the transfusion-sparing effect of intravenous iron supplementation.

We suggest that treatment with erythropoietin may correct anaemia more rapidly than treatment with folic acid and iron. 2C

Alternatives to RBC transfusion for maintaining haemoglobin concentrations are required. Patients with moderate (Hb < 9.5 g dl⁻¹) to severe (Hb < 8.5 g dl⁻¹) anaemia may benefit from intravenous iron therapy, 757–763 which elicits more rapid recovery from shorter treatment compared with oral therapy. 758–763 Intravenous iron may also improve fatigue score, but not overall quality life assessment, up to 12 weeks postpartum. 763 No evidence was identified comparing different intravenous iron therapies, and the safety of iron carboxymaltose requires further investigation. 764 In addition, the transfusion-sparing potential of intravenous iron remains unclear. 269

Co-administration of erythropoietin and iron has been advocated for treating postpartum anaemia. 763,766 Treatment should begin within 96 h and appears to be safe. 767 Increased haemoglobin concentration has been reported following treatment of anaemic (Hb < 10 g dl⁻¹) parturients with erythropoietin and oral or intravenous iron, 767 although this evidence is from a small patient population. Erythropoietin and iron may be used to treat patients with severe anaemia (Hb < 8 g dl⁻¹) and pronounced clinical symptoms or rejection of donor blood. 757

8.2.2.2 Postpartum haemorrhage: coagulation monitoring and management

Acquired obstetric coagulopathy affects approximately 21% of deliveries, with complications including PPH requiring transfusion, 725 increased risk of placental abruption, 768 placenta praevia and accreta, 769 amniotic fluid embolism, 741,770 retained dead fetus 771 and posthaemorrhagic shock. 772,773 Obstetric conditions also account for 1–5% of clinical cases of DIC. 774 In this section, we evaluate the evidence for coagulation monitoring in severe obstetric bleeding.

Fibrinogen measurement

Recommendations

We suggest assessing fibrinogen concentration in parturients with bleeding, as concentrations <2 g l⁻¹ may identify those at risk of severe PPH. 2C

Plasma fibrinogen concentrations increase during pregnancy to a normal third-trimester range of 4.5–5.8 g l⁻¹. 772 Fibrinogen concentrations decrease with increasing blood loss and may serve as a marker of haemostatic impairment. 85,776,777 Plasma fibrinogen concentration below 2 g l⁻¹ is associated with the development of severe PPH, comprising a decrease in haemoglobin by ≥4 g dl⁻¹, transfusion of ≥4 U RBCs, requirement for haemostatic intervention (angiographic embolisation, surgical arterial ligation or hysterectomy) and death. 414 Evaluation of fibrinogen concentration at the onset of labour is of less predictive value. 778

Platelet count

Recommendation

Platelet count <100 x 10⁹ l⁻¹ at the onset of labour, particularly combined with plasma fibrinogen concentration <2.9 g l⁻¹, may indicate an increased risk of PPH. C

Platelet count <100 x 10⁹ l⁻¹ at the onset of labour is associated with increased risk of PPH and is exacerbated by plasma fibrinogen concentration <2.9 g l⁻¹. 777 Platelet count during the ninth month of pregnancy does not correlate with platelet count at the onset of labour. 778 A single platelet count does not predict development of severe PPH. However, severe PPH typically involves a time-dependent decrease in platelet count, whereas non-severe PPH usually involves a stabilisation of platelet count during the first 24 h of bleeding. 414 Low platelet count is associated with increased RBC and FFP transfusion. 87
Activated partial thromboplastin time and prothrombin time

**Recommendation**
aPTT and PT are of little predictive value for PPH. C

aPTT and PT are poor predictors of severe PPH.414 aPTT, but not PT, shows a small but significant correlation with estimated blood loss in PPH, while increased PT and aPTT are associated with greater RBC and FFP transfusion requirements.87

**Thrombelastography or thromboelastometry**

**Recommendation**

Thromboelastometry can identify obstetric coagulopathy and hyperfibrinolysis and guide haemostatic therapy. C

FIBTEM, a bedside thromboelastometric fibrin clot quality test, provides results in 5–15 min and can indicate a reduced contribution of fibrinogen to clot strength.779 FIBTEM maximum clot firmness is significantly decreased during PPH.

Thromboelastometric measurements can identify the hypercoagulability seen in normal pregnancy775 and also in caesarean section,780,781 pre-eclampsia and HELLP syndrome.782 They can potentially allow rapid recognition of hyperfibrinolysis and guide therapy with tranexamic acid, fibrinogen concentrate, PCC, FFP and platelets.770

**Hyperfibrinolysis**

Overall fibrinolytic capacity decreases during pregnancy,783,784 although there is little evidence of hyperfibrinolysis in severe PPH versus non-severe PPH.414 Hyperfibrinolysis is associated with obstetric coagulopathic complications including shock, DIC and amniotic fluid embolism.770

8.2.2.3 Haemostatic treatment of obstetric haemorrhage

During normal pregnancy, maternal haematological adaptation includes anaemia, neutrophilia, mild thrombocytopenia, increased levels of procoagulant factors and diminished fibrinolysis.722 Here, we assess the specific perioperative transfusion requirements of obstetric patients due to pregnancy related haematological changes.

What are the indications for transfusion with fresh frozen plasma and platelets?

**Recommendation**

In life-threatening PPH, we suggest a transfusion protocol with a fixed product ratio or individualised procoagulant intervention and factor substitution. 2C

A single centre US study reported that 0.87% of US deliveries involve transfusion with haemostatic blood products.727 Approximately 1.25 in 1000 deliveries are complicated by major obstetric haemorrhage (requirement of >5 U RBCs).731 RBC transfusion is accompanied by FFP and platelet transfusions in 20% and 16% of cases, respectively.736 Transfusion of FFP, platelets and cryoprecipitate may be a marker for bleeding severity and volume of RBCs required.231 An algorithm for managing obstetric haemorrhage783 suggests transfusion with FFP if INR is >1.5, with platelets if the platelet count is <25 000 μl−1, and with cryoprecipitate if fibrinogen concentration is <100 mg dl−1. For uncontrolled, life-threatening haemorrhage, a multitransfusion protocol is recommended: 6 U RBCs, 4 U FFP and 1 U platelets.785 Others advocate ROTEM-based assessment or damage control resuscitation (RBC:FFP:platelet ratio of 1:1:1) for management of placenta accreta requiring multiple transfusions.786

Rapid haemostatic surgery avoiding hypothermia and using intravenous saline may enhance survival in a low-resource setting, based on data showing that 88% of Jehovah’s Witnesses survived haemorrhagic shock following uterine rupture.787

What are the indications for fibrinogen substitution with fibrinogen concentrate or cryoprecipitate?

**Recommendation**

Considering physiologically elevated fibrinogen concentrations in pregnancy, we suggest that a higher trigger value for treating hypofibrinogenaemia may be required. C

Fibrinogen concentrations are typically elevated (approximately 5 g l−1) in pregnancy,775, so the potential for FFP (which has an average fibrinogen concentration of 2.5 g l−1)581 to supplement fibrinogen concentration is limited. Fibrinogen concentrate represents an alternative therapy, and empirical use in bleeding patients (8–33% obstetric) has indicated potential reductions in blood loss and transfusion requirements.426,583,584,726,788 Trigger levels for fibrinogen substitution vary between 1 and 2 g l−1, with a mean administered dose of 2–4 g.426,583,584,726,788 Studies investigating cryoprecipitate in obstetric patients were not identified.

No serious adverse events were reported with fibrinogen concentrate in the obstetric setting, although one study associated haemostatic treatment (including fibrinogen substitution) with an increased risk of venous thrombosis.726

What are the indications for the use of antifibrinolytic therapies (tranexamic acid) in obstetrics?

**Recommendations**

We recommend the administration of tranexamic acid in obstetric bleeding to reduce blood loss, bleeding duration and the number of units transfused. 1B

We suggest that tranexamic acid be considered before caesarean section. 2C

In antepartum bleeding, we suggest administration of tranexamic acid. 2B
To balance the procoagulant effects which occur naturally during delivery, fibrinolysis is also increased. However, abnormal fibrinolysis is associated with complications including placental abruption and antepartum bleeding, and amniotic fluid embolism.

Antifibrinolytic therapy, used prophylactically for vaginal or caesarean delivery, or when postpartum bleeding evolves, may prevent such complications. Several studies suggest that tranexamic acid administered 10–20 min before caesarean section may reduce perioperative blood loss. Tranexamic acid may reduce antepartum bleeding in placental abruption and placenta praevia, and appears safe during pregnancy and postpartum.

In a recent study, tranexamic acid reduced blood loss and 42-day transfusion requirements in PPH. No severe side-effects (e.g. thromboembolic complications) were observed, although the study was not powered to assess safety. Mild transient adverse manifestations such as nausea, vomiting, dizziness and ‘seeing stars’ occurred more frequently in the tranexamic acid group than in the control group, possibly due to the relatively high dose used in this trial (4 g).

What are the indications for other coagulation factor concentrates (prothrombin complex concentrate and factor XIII)?

In a case of amniotic fluid embolism following vaginal delivery, stable clotting was achieved by thromboelastometry-guided coagulation therapy comprising tranexamic acid, fibrinogen concentrate, platelets and PCC, as well as RBC and FFP in a 1:1 ratio. No further reports were retrieved describing PCC or FXIII therapy in obstetric patients with non-inherited coagulation deficiency.

What are the indications for the use of recombinant factor VIIa?

Recommendations

We recommend that rFVIIa should only be considered as last-line therapy because of its thromboembolic risk.

We suggest that fibrinogen concentration and number of platelets should be optimised before administration of rFVIIa.

rFVIIa can be considered as second-line haemostatic therapy alongside intrathecal tamponade, uterine compression sutures, pelvic vessel ligation and interventional radiology. Case reports and retrospective studies support off-label use of rFVIIa for severe obstetric coagulopathic bleeding. Subjective evaluation has shown rFVIIa administration to arrest bleeding in 75–92% of cases. rFVIIa may also prevent postpartum hysterectomy, although other studies do not support this finding. Administration of rFVIIa may not decrease transfusion requirements, although this may reflect its frequent use in complex coagulopathic bleeding. Plasma fibrinogen concentration and platelet count should be optimised before administration of rFVIIa.

Administration of rFVIIa was potentially linked to three thromboembolic events in a study including 110 otherwise healthy obstetric patients, and its use in PPH has been associated with lower limb ischaemia and pulmonary embolism, albeit with favourable clinical outcomes. Although rFVIIa potentially carries a thromboembolic risk, no difference in mortality has been identified in other patient categories.

8.3 Orthopaedic surgery and neurosurgery

8.3.1 Bleeding risk of different orthopaedic and neurosurgical procedures

Recommendation

In elective orthopaedic surgery, we recommend the implementation of a blood transfusion protocol (algorithm), together with staff education.

There is a lack of standardised definitions for the reporting of bleeding events. Therefore, the incidence of bleeding and severe bleeding differs remarkably between studies. Orthopaedic surgery is often associated with clinically relevant bleeding and the need for allogeneic blood transfusion. The implementation of a blood transfusion protocol (algorithm) together with staff education, based on early preoperative detection and treatment of anaemia, perioperative blood salvage and retransfusion, and a restrictive transfusion trigger, has been shown to reduce allogeneic blood transfusion and the need for preoperative autologous blood donation.

Severe bleeding with the need for allogeneic blood transfusion is relatively uncommon in neurosurgery (affecting 6.7% of patients undergoing neurosurgery in 2010 at University Hospital Essen, Germany; unpublished observations). However, haematoma growth has a major impact on neurological outcomes and mortality in patients with intracerebral haemorrhage (ICH). Therefore, ICH has to be treated early.

Recommendation

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections.

Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections such as wound infection and pneumonia, increased length of hospital stay, and increased hospital costs.

Recommendation

Infusion of colloids in patients with severe bleeding can aggravate dilutional coagulopathy by additional effects on fibrin polymerisation and platelet aggregation.
Coagulopathy in patients undergoing orthopaedic surgery is usually caused by pre-existing coagulation disorders, medication with oral anticoagulants or antiplatelet drugs, or dilutional coagulopathy due to severe blood loss and volume resuscitation with crystalloids and colloids. Colloids, and especially high molecular weight hydroxyethyl starch (HES) solutions, have dose-dependent effects on fibrin polymerisation and platelet aggregation, aggravating coagulopathy.

**8.3.2 Bleeding risk due to pre-existing coagulation disorders and medications**

**Recommendations**

*We recommend that, for orthopaedic surgery, monotherapy with aspirin does not need to be discontinued. 1B*

*We recommend discontinuing dual antiplatelet therapy before urgent intracranial neurosurgery. A risk-benefit analysis is required for the continuation of aspirin monotherapy during neurosurgery. 1B*

COX-2 selective NSAIDs do not increase perioperative blood loss in patients undergoing total knee arthroplasty. Therefore, it is not necessary to discontinue these drugs before surgery. In contrast, ibuprofen, diclofenac and indomethacin significantly increase perioperative blood loss in total hip arthroplasty. Therefore, discontinuation of non-selective NSAIDs is advised.

Pretreatment with daily low-dose aspirin was associated with a small increase in postoperative transfusion but no major bleeding in patients undergoing proximal femoral fracture surgery. Neither aspirin nor clopidogrel monotherapy needs to be discontinued before urgent orthopaedic surgery, and surgery should not be delayed in patients receiving such treatment.

Recent studies examining the effect of prior antiplatelet therapy on outcome in patients with spontaneous ICH have shown conflicting results. A large, prospective trial demonstrated that antiplatelet medication at ICH onset was not associated with increased haemorrhage volumes, haemorrhage growth, or clinical outcome at 90 days. However, the combination of aspirin and clopidogrel compared to clopidogrel alone after recent ischaemic stroke or transient ischaemic attack has been associated with an increased risk of bleeding events. Antiplatelet therapy, and especially dual antiplatelet therapy, has also been associated with an increased risk of ICH after fibrinolytic therapy in patients with ischaemic stroke. A third study suggested that antiplatelet medication may potentially increase ICH volume. A meta-analysis and systematic literature review reported that antiplatelet therapy at the time of ICH increased mortality but had no effect on functional outcome. Prasugrel is associated with an increased risk of major/fatal bleeding, compared to clopidogrel. Compared to clopidogrel, ticagrelor has been shown to significantly reduce the rate of death from vascular causes, myocardial infarction or stroke, without increasing major bleeding.

In another study, there was no significant difference between ticagrelor and clopidogrel in the risk of stroke; however, intracranial bleeding was more common with ticagrelor.

In summary, monotherapy with aspirin or clopidogrel seems not to be associated with a significantly increased risk of ICH or haematoma growth, but dual antiplatelet therapy, therapy with prasugrel, or a combination with other risk factors such as fibrinolytic therapy or VWD increase the risk of ICH and subsequent haematoma growth. Therefore, dual antiplatelet therapy should be discontinued before urgent intracranial neurosurgery. There is need for a risk-benefit analysis of the continuation of aspirin monotherapy during neurosurgery.

**Recommendation**

*We recommend against performing orthopaedic surgery during the first three months after bare metal stent implantation or during the first twelve months after drug-eluting stent implantation. 1C*

Following bare metal stent implantation or drug-eluting stent implantation, elective orthopaedic surgery should not be performed during the first three months or twelve months respectively, because surgery results in a prohaemostatic condition and increases the risk of stent thrombosis.

**8.3.3 Screening tests to predict bleeding in orthopaedics and neurosurgery**

**Recommendation**

*Preoperative medication with ADP receptor antagonists or with new oral anticoagulants is associated with an increased risk of major bleeding and ICH, especially if used in combination. B*

Preoperative administration of ADP receptor antagonists such as clopidogrel, prasugrel and ticagrelor, or new oral anticoagulants such as dabigatran, rivaroxaban and apixaban is associated with an increased risk of major bleeding and ICH, especially if used in combination. Of note, these drugs cannot be monitored with conventional coagulation screening tests such as aPTT, PT and platelet count.

**Recommendation**

*Reduced platelet activity is associated with early haematoma growth, more intraventricular haemorrhage and worse 3-month outcome following ICH. C*

Conflicting evidence exists as to whether the direct thrombin inhibitor dabigatran enlarges haematoma volume in experimental ICH. However, a recent case report has reported the development of an epidural haematoma and severe intraoperative haemorrhage in a spine trauma patient on dabigatran. Furthermore,
neuraxial blockade is contraindicated in patients on dabigatran, even 34 h after withdrawal of the drug.903

Conflicting data also exist regarding whether or not prior antplatelet therapy has an impact on haemorrhage growth or outcome after ICH and traumatic brain injury.880,881,884,901,905 A recently published meta-analysis including a 25 cohort multivariate analysis showed that antplatelet therapy at the time of ICH, compared to no antplatelet therapy, was independently associated with increased mortality but not with poor functional outcome.885 Furthermore, cerebral microbleeds are a potential risk factor for ICH in patients treated with antplatelet drugs or warfarin.906–908

The efficacy of platelet transfusion in patients on antplatelet therapy suffering from ICH or traumatic brain injury is also currently under discussion.880,906–911 Conflicting data exist concerning the impact of antplatelet drugs on ICH growth on one hand, and the efficacy of platelet transfusion to stop bleeding on the other, and can in part be explained by the variable response to antplatelet drugs. Several authors reported a close correlation between platelet function testing using ADP as an activator in whole blood impedence aggregometry (Multiplate) or whole blood turbidimetric aggregometry (VerifyNow) and bleeding complications, transfusion requirements for platelet concentrates and outcome after ICH.912–916 In addition, reduced platelet activity has been associated with early haematoma growth, more intraventricular haemorrhage and worse 3-month outcome after ICH.917,918 Therefore, point-of-care testing of platelet function may be helpful to detect platelet dysfunction in patients with ICH or prior to neuraxial surgery or blockade, and to guide corresponding therapy.914,919–922 Also, thrombin time and ecarin clotting time may be helpful to identify emergency patients treated with oral direct thrombin inhibitors such as dabigatran.906,908,923

Recommendation

Low platelet count, low plasma fibrinogen concentration and FXIII deficiency are predictive of bleeding complications in ICH, intracranial surgery and major spine surgery, particularly when they occur in combination. C

In a multivariate analysis of predictors of haematoma enlargement in spontaneous ICH, a low concentration of fibrinogen (2.41 ± 0.08 g l–1 vs. 2.86 ± 0.04 g l–1 in patients with and without haematoma growth, respectively) was the only haematological parameter shown to be an independent predictor of haematoma growth, with an odds ratio of 0.74 for one standard deviation change (0.09 g l–1; P = 0.042).924

Most guidelines recommend a transfusion threshold of 100 000 µl–1 platelets in patients undergoing neurosurgery, based on expert opinion.925–929 However, in a prospective observational study in patients undergoing intracranial surgery, a postoperative platelet count below 150 000 µl–1 was associated with a 2.5-fold increase in relative risk of postoperative haematoma requiring revision surgery, and in combination with FXIII activity <60%, the relative risk for haematoma increased to 9.7.410 In the same study, preoperative FXIII activity <80% was associated with a 3.9-fold increase in relative risk of postoperative haematoma requiring revision surgery, which increased to 6.4-fold for postoperative FXIII activity <60%.410 The third risk factor was fibrinogen concentration of <3.0 g l–1 preoperatively or <1.5 g l–1 postoperatively, with a 2.9- and 2.5-fold increased relative risk of postoperative haematoma respectively. The highest relative risk of postoperative haematoma (12.2-fold) was achieved with the combination of a postoperative FXIII activity <60% and fibrinogen concentration <1.5 g l–1. A postoperative prolongation of PT (<60% activity compared to normal; relative risk, 6.2) or aPTT (>35 s; relative risk, 4.8) had less impact on the relative risk for postoperative haematoma, even in combination with low FXIII activity (<60%).410

FXIII activity cannot be measured by conventional coagulation screening tests. Of note, in a study determining the effect of colloid infusion (HES 200/0.5 or modified gelatin 4%) on haemostasis in patients undergoing knee replacement surgery, the activity of FXIII decreased from 89.0 to 58.5%.960 Acute diffuse postoperative bleeding due to acquired FXIII deficiency has also been reported after free flap operations in plastic surgery.938 Furthermore, there are several case reports dealing with spontaneous subdural haematomas or recurrent spontaneous ICH in children and young adults related to FXIII deficiency.931–933 Prophylactic therapy with a FXIII concentrate in young patients with congenital FXIII deficiency was associated with a marked decrease of bleeding episodes.934–936 Furthermore, some FXIII polymorphisms are associated with an increased risk of aneurysmal subarachnoid haemorrhage.937,938 In summary, FXIII seems to play an important role in postoperative bleeding complications in neurosurgery.

Recommendation

Preoperative measurement of plasma fibrinogen concentration provides more information on bleeding volume and transfusion requirements than standard screening tests. C

Preoperative plasma fibrinogen concentration has been shown to be strongly associated with increased perioperative bleeding and transfusion requirements (>2 U RBC) in scoliosis surgery.939 In this prospective observational study, total blood loss correlated significantly with preoperative fibrinogen concentration but with neither platelet count, aPTT nor PT. Patients with blood loss in the upper quartile had significantly lower preoperative
In some RCTs, a second anticoagulation was started after the initial treatment, whereas in comparison, the intensity of oral anticoagulation was the same in both groups in this study.

8.3.4 Antifibrinolytics

Recommendations

We suggest administering tranexamic acid in total hip arthroplasty, total knee arthroplasty, and major spine surgery. 2A

Tranexamic acid may promote a hypercoagulable state for some patients (with pre-existing thromboembolic events, hip fracture surgery, cancer surgery, age over 60 years, women). Therefore, we suggest an individual risk-benefit analysis instead of its routine use in these clinical settings. 2A

Antifibrinolytic medication has been shown to reduce perioperative blood loss, allogeneic blood transfusions and associated costs in major orthopaedic surgery such as total hip or knee arthroplasty. 477,953−955 Although concerns exist about increased thrombotic events with the use of these agents, large meta-analyses suggest that tranexamic acid can be employed safely and efficaciously to decrease perioperative blood loss and transfusion requirements without increased risk of thromboembolic complications in major orthopaedic surgery. 480,534,645,953,954−958

However, further studies are needed to clarify the neurological risk, appropriate indications and dosing of tranexamic acid. 953 In addition, the use of antifibrinolytics in patients with cancer cannot be recommended, because no beneficial effect has been shown and the risk of thromboembolic complications may be increased. 959−960 Tranexamic acid may also promote hypercoagulability following pre-existing thromboembolic events and hip fracture surgery, in patients over 60 years, and in women. 961

Data showing favourable efficacy and safety are best for tranexamic acid. 480,954,962 whereas in comparison, the data for EACA are sparse. 477,529,531,963−967 In several RCTs, hip/knee replacement patients received tranexamic acid as a single preoperative intravenous bolus dose of 10−15 mg·kg⁻¹·h⁻¹ 530,968−972 In some RCTs, a second dose was given 3 h later or at the time of tourniquet deflation, 531,973−975 while in others a continuous infusion of 1 mg·kg⁻¹·h⁻¹ was started after the initial bolus 530,976−979 Oral administration of tranexamic acid (1 g preoperatively and then every 6 h for 18 h postoperatively) has also been shown to be effective in patients with total knee replacement. 980 In hip fracture surgery, tranexamic acid (15 mg·kg⁻¹ as a single or double bolus dose at surgical incision and 3 h later) reduces allogeneic blood transfusions.

**Recommendation**

We suggest the use of viscoelastic tests (ROTEM/TEG) for monitoring perioperative haemostasis in major orthopaedic surgery and neurosurgery. 2C

Hypocoagulability in thrombelastography (prolonged r and k time, reduced ø-angle and maximum amplitude) has been shown to be associated with an increased incidence of bleeding complications in paediatric neurological patients, whereas standard coagulation tests (platelet count, PT, aPTT, and plasma fibrinogen) were normal. 940 However, pre-, intra- and postoperative fibrinogen concentrations were >3 g·l⁻¹ in both groups in this study. In several studies, thromboelastometry (FIBTEM test) has been shown to successfully diagnose fibrinogen deficiency, as well as fibrin polymerisation disorders, such as those induced by colloid infusion or dysfibrinogenemia. 30,40,123,427,862,864,941−943

**Recommendation**

The intensity of oral anticoagulation with warfarin, measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular with ICH. C

The incidence of ICH in patients on oral anticoagulation with warfarin has been reported at 0.1%−3.7% per patient-year, and the incidence of major bleeding at 1.2−13.1% per patient-year. Independent risk factors for major bleeding and ICH have been identified as the indication for oral anticoagulation (e.g. atrial fibrillation or cerebral ischaemia), the patient’s age (<65, 66−85 or >85 years) and the intensity (INR) and duration of anticoagulation. 944−950 Patients anticoagulated with warfarin because of cerebral ischaemia had 19 times the risk of ICH compared to patients with atrial fibrillation. 945 The incidence of ICH was twice as high for patients >65 years of age, and around two times higher again in patients >85 years of age. 945,947 An INR of 1.6−2.0 was associated with insufficient anticoagulation, whereas an INR of 2.0−3.0 is considered as effective and safe. 946,948 However, the incidence of ICH increased significantly with INR values >3.0. 946−949,951 here, the incidence of ICH increased by a factor of 1.37 for each increase of INR by 0.5, and the risk for death increased 2.3 times for each increase of INR by 1. 945,949 Furthermore, patients with INR >3.0 had a significantly greater haematoma volume and a higher mortality. 952 In summary, the intensity of oral anticoagulation with warfarin, measured by INR, shows a close correlation to the incidence and severity of bleeding complications, in particular to ICH.
blood transfusion but may promote hypercoagulability. Thus, further safety evaluation is required before recommending routine use of tranexamic acid in this setting. In several RCTs performed in children and adults undergoing scoliosis/spine surgery, a loading dose of 10–30 mg kg\(^{-1}\) tranexamic acid followed by a continuous infusion of 1 mg kg\(^{-1}\) h\(^{-1}\) has been shown to be effective and well tolerated. EACA has been administered to scoliosis surgery patients (loading dose 100 mg kg\(^{-1}\) followed by 10 mg kg\(^{-1}\) h\(^{-1}\) until the end of surgery).\(^{666}\)

In neurosurgery, 1 g tranexamic acid immediately after the diagnosis of aneurysmal subarachnoid haemorrhage, followed by 1 g every 6 h until the aneurysm was occluded, reduced mortality from early rebleeding by 80%. However, data on the efficacy and safety of antifibrinolytics in intracranial surgery are sparse and relate mainly to aprotinin, which was withdrawn in 2007.\(^{985}\)

### 8.3.5 Recombinant activated factor VIIa

**Recommendations**

*We suggest the use of rFVIIa in patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery. 2C*

Prophylactic use of rFVIIa does not reduce perioperative blood loss or transfusion in non-haemophilic and non-coagulopathic patients undergoing major orthopaedic surgery or neurosurgery, and it may increase the incidence of thromboembolic events. Therefore, we recommend against the prophylactic use of rFVIIa in these clinical settings. 1B

*We recommend restricting off-label use of rFVIIa to patients with severe bleeding who are unresponsive to other haemostatic interventions. 1C*

Continuous infusion of rFVIIa (initial preoperative bolus of 90 mg kg\(^{-1}\) followed by a continuous infusion of 50 mg kg\(^{-1}\) h\(^{-1}\) for a median of 20 days) was effective and well tolerated in a prospective study of patients with neutralising antibodies to FVIII undergoing elective major orthopaedic surgery. Postoperative bleeding was controlled by an additional single bolus of 60 mg kg\(^{-1}\) rFVIIa.\(^{986}\) A recently published consensus protocol for the use of rFVIIa in elective orthopaedic surgery in haemophilic patients with inhibitors recommended an initial bolus dose of rFVIIa in the range of 120–180 mg kg\(^{-1}\) to cover surgery and concomitant use of antifibrinolytic agents and fibrin sealants.\(^{987}\) Conversely, there is a lack of evidence to suggest that rFVIIa might be effective and well tolerated in severe intractable bleeding during spinal surgery.

rFVIIa reduced intraoperative transfusion requirement for RBCs in 26 adolescent patients with scoliosis, who received rFVIIa perioperatively.\(^{988}\) Other studies have shown that a small dose of rFVIIa (20 μg kg\(^{-1}\)) reduced PT and aPTT but did not significantly reduce blood loss. Moreover, the drug failed to produce a significant reduction in blood loss or transfusion volume in an RCT in 49 spinal surgery patients.\(^{991}\) One patient with advanced cerebrovascular disease who received 300 mg kg\(^{-1}\) rFVIIa died six days after surgery due to an ischaemic stroke. In addition, there was also no significant reduction in perioperative blood loss or transfusion of blood components in a randomised, placebo-controlled trial including 48 patients undergoing major pelvic-acetabular surgery.\(^{992}\) Therefore, there is little evidence to suggest that prophylactic rFVIIa reduces perioperative blood loss or transfusion requirements in major orthopaedic surgery.

In studies of non-haemophilic, coagulopathic neurosurgical patients, 40–120 mg kg\(^{-1}\) rFVIIa rapidly normalised PT (baseline INR > 2) and aPTT within 20 min;\(^{993–995}\) this allows a shorter transit time to intervention/craniotomy.\(^{996,997}\) Although rFVIIa can reduce the change in ICH volume, no significant effect on mortality, modified Rankin Scale score or extended Glasgow Outcome Scale score has been demonstrated.\(^{555,557,998–1000}\) However, a significant increase in thromboembolic adverse events has been observed with rFVIIa (e.g. myocardial infarction, stroke), especially in elderly patients and those with pre-existing vascular diseases.\(^{554–557,717,981,999,1001–1003}\) Furthermore, there is no reliable evidence that haemostatic drugs are effective in reducing mortality or disability in patients with traumatic brain injury.\(^{981,1004–1007}\) Therefore, the use of rFVIIa in paediatric patients with brain tumours should be restricted to patients with life-threatening bleeding who are unresponsive to conventional treatment.\(^{1008,1009}\)

### 8.3.6 Prothrombin complex concentrate and new oral anticoagulants

**Recommendations**

*In patients with INR > 1.5, with life-threatening bleeding or ICH, we recommend that four-factor PCCs (20–40 U kg\(^{-1}\)), supplemented with vitamin K (10 mg by slow intravenous infusion), should be used for rapid reversal of VKAs. 1C*

*In patients with neutralising antibodies to FVIII undergoing major orthopaedic surgery, we suggest using activated PCCs (e.g. FEIBA, FVIII inhibitor bypassing agents). 2C*

New oral anticoagulants, such as rivaroxaban and dabigatran, may increase surgical bleeding and ICH growth. We suggest that PCC, FEIBA or rFVIIa may be used as non-specific antagonists in life-threatening bleeding or ICH. 2C

For life-threatening bleeding or ICH among oral anticoagulation patients receiving VKAs, for INR > 1.5,
guidelines recommend PCCs or rFVIIa for immediate reversal of INR, with co-administration of vitamin K (10 mg by slow intravenous infusion).**45,56,59,98,1010–1015** Despite consistency between recommendations, adherence to them is poor in several countries where FFP is used instead of PCC.**39,59,1016–1020** These data indicate a requirement for education in this field,**1019** potentially including information on the three different types of PCC available with different compositions and different indications.**594,59,1021,1022** Four-factor PCCs are most effective for rapid reversal of VKA-induced anticoagulation because they replace all four vitamin K-dependent coagulation factors (II, VII, IX, and X), and some of them also contain inhibitors such as protein C, S, and Z.**341,1023** Three-factor PCCs are used to treat haemophilia B (in the US) and are used for warfarin reversal where four-factor PCCs are not available (e.g. in Australia). Three-factor PCCs contain little FVII and are less effective in correcting INR.**59,1028–1030** Activated PCCs such as FEIBA® (Baxter Healthcare Corp, USA; FVIII inhibitor bypassing agent) are indicated in patients with haemophilia and antibodies (inhibitors) against FVIII or FIX.**1031–1033** At a median initial dose of 100 U kg⁻¹, FEIBA has been shown to be effective, well tolerated (low incidence of thromboembolic events) and cost-effective in patients with FVIII/FIX inhibitors undergoing major orthopaedic and other surgery.**1034–1038** However, activated PCCs are not used for rapid reversal of VKA-induced anticoagulation.

Compared with FFP, which takes 14–50 h to correct INR, four-factor PCCs provide quicker and more controlled correction of INR (a target INR of 1.2–1.4 can be achieved within 3–30 min) and improved bleeding control.**402,449,586–588,59,590,591,594,59,906,1014–1015,1017,1021,1030,1039–1043** Recommended doses for emergency VKA reversal in the presence of ICH are 20–40 IU kg⁻¹ PCC (0.8–1.6 ml kg⁻¹; fixed or calculated from body weight, baseline and target INR), 15–120 μg kg⁻¹ rFVIIa or 15–30 ml kg⁻¹ FFP.**403,591,1012,1014** Transfusion-associated circulatory overload and subsequent acute lung injury complications, which occur in 1–8% of hip/knee arthroplasty patients receiving FFP, can be avoided by using PCC.**141,400,1016,1043–1045** The incidence and extent of haematoma growth are significantly lower in patients receiving PCCs compared with FFP and vitamin K.**120** which is attributable to more rapid reversal of INR. Haematoma growth is associated with poor neurological outcome, and aggressive management of VKA-associated ICH with rapid INR correction appears to translate into improved outcomes following ICH.**1050** However, this is yet to be proved by well-designed RCTs.**1051,1052**

For rapid reversal of VKAs, studies have shown that PCCs have a favourable safety profile, with a low incidence of thromboembolic events.**449,587,588,590,591,596,633,1023,1024,1040,1042,1053,1054** In a recent meta-analysis, only 12 patients (1.4%) treated with PCCs for VKA reversal had a thromboembolic event, of which two were fatal.**1055** The incidence of thromboembolic events was 1.8% in patients treated with 4-factor PCCs and 0.7% in patients treated with 3-factor PCCs, and these data are consistent with other reviews and pharmacovigilance data.**1022,1056** The occurrence of thromboembolic events is not surprising because VKAs are prescribed to patients with a high risk of thrombotic events.**596,1022,1054,1055,1057** Excessive substitution with PCCs should be avoided, and accurate monitoring of coagulation status may allow thrombotic risk to be reduced.**1025,1058,1059** Four patients (1.9%) treated with a solvent/detergent-treated and nanofiltered four-factor PCC have shown seroconversion for parvovirus B19.**588,590,1055** No other cases of viral transmission or infectious complications after administration of PCCs have been published during the last 15 years.**1043,1055–1057**

In contrast to rFVIIa (100 μg kg⁻¹), 4-factor PCCs (20–40 μg kg⁻¹) not only correct PT, INR and lag time in endogenous thrombin potential, but they also normalise thrombin generation and activity of coagulation factors II, VII, IX and X, while additionally shortening bleeding time and reducing blood loss.**454,1060–1062** A higher dose of PCC (50 μg kg⁻¹) may induce hypercoagulable thrombin generation, potentially increasing the risk of thromboembolic events.**1059,1061** This underlines the need to avoid excessive substitution with PCCs, and may be particularly important in bleeding patients with coagulation factor deficiency due to liver dysfunction.**120,420,457,458,1063–1068** Based on point-of-care thromboelastometric results, four-factor PCCs have been used in combination with fibrinogen concentrate in several cohort studies in trauma, neurosurgery, cardiac surgery, visceral surgery and liver transplantation.**118,120,420,457,458,1066** These studies show significant reductions in transfusion requirements, transfusion-associated adverse events, and thromboembolic events with PCC; however, prospective RCTs are needed for confirmation.

The recent approval of new oral anticoagulants, such as rivaroxaban and dabigatran, is changing the therapeutic landscape.**1057,1069–1072** These drugs may hamper haemostatic management because they cannot be monitored by simple conventional laboratory assays, their pharmacokinetics vary significantly between patients (in particular dependent on age and renal function), they may increase surgical bleeding and ICH growth, and they have no validated antagonists.**893,1073–1080** In some animal models, rFVIIa, FEIBA and PCC partially improved laboratory parameters in animals treated with fondaparinux, rivaroxaban or dabigatran, but it is unclear whether these drugs would be effective in treating bleeding patients.**898,900,1081–1084**


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8.4 Visceral and transplant surgery
8.4.1 Should coagulopathy associated with chronic liver disease be corrected before invasive procedures?

Haemostatic changes coinciding with liver disease were traditionally thought to confer bleeding diathesis. Recent data challenge this theory, leading to a concept of ‘re-balanced haemostasis’ in patients with chronic liver disease (CLD). 1085,1086

8.4.1.1 What is the evidence that haemostasis is ‘re-balanced’ in CLD?

Recommendation

Despite PT, aPTT and INR indicating coagulopathy in CLD, global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable CLD. 1C

In CLD, procoagulant concentrations are typically decreased (except FVIII, which is elevated). However, most endogenous anticoagulants (antithrombin, proteins C and S) are also depleted, 1087 maintaining haemostatic balance. Thrombin generation in stable liver disease is similar, or elevated, compared with healthy individuals. 1087,1088

CLD patients often exhibit thrombocytopenia and platelet adhesion/aggregation abnormalities. These changes may be counterbalanced by increased VWF levels and reduced VWF-cleaving activity of ADAMTS 13. 1089 Platelet hyperactivity has been reported in cholestatic liver disease. 1090,1091

Elevated fibrinolysis and clot instability are balanced by increased plasminogen activator inhibitor (PAI-1) levels. PAI-1 levels are high in acute liver failure and cholestatic liver disease; clinically significant fibrinolysis is rare in both conditions. 1092,1093

‘Re-balanced’ haemostasis in CLD is reflected in the increasing number of CLD patients undergoing major abdominal surgery without requiring transfusion. 1094 However, as venous thromboembolic events are common in cirrhotic patients, they cannot be considered ‘autoanticoagulated’. 1095

8.4.1.2 What is the evidence that INR reflects bleeding risk in patients with chronic liver disease?

Recommendation

Mild to moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. 1C

PT, aPTT and INR are widely used to assess CLD patients preoperatively, although evidence that these parameters predict bleeding risk is poor. 91 Massicotte et al. 1094 reported that INR does not predict OLT transfusion requirements and that preoperative INR correction is unnecessary. Observational studies suggest that OLT can be performed without FFP transfusion; 1096 this may be advantageous in avoiding volume overload. 1097

PT and INR do not reflect bleeding risk in CLD, as the concurrent anticoagulant reduction is not assessed. 1098

Thrombin generation is similar in healthy and cirrhotic individuals, and there is no definite association between INR and bleeding risk among liver disease patients. 1099

In addition, INR values may vary between laboratories, so defining cut-off values is problematic. 1100

8.4.1.3 Should FFP be used to correct prolonged INR before invasive procedures?

Recommendation

We recommend against the use of FFP for preprocedural correction of mild-to-moderately elevated INR. 1C

Implementation of practice guidelines is recommended to prevent inappropriate transfusion. 1101 Evidence suggests that FFP should not be administered to non-bleeding patients when INR is 2. Although PT and INR are often used to guide FFP transfusion, no correlation has been established between degree of coagulopathy and transfusion outcome, 16 nor has optimal FFP dosing been determined.

No randomised studies with clinical endpoints have investigated the effectiveness of FFP transfusion in CLD. Current evidence suggests no benefit in correcting mild-to-moderate INR elevations before invasive procedures in CLD patients.

8.4.1.4 What level of thrombocytopenia should be tolerated in CLD?

Recommendation

We suggest a platelet count of 50 000 µL⁻¹ as a threshold for platelet transfusion before liver biopsy. 2C

The evidence supporting platelet count cutoff values is limited. Moreover, platelet count does not represent platelet function. Current consensus, 1099 with supporting evidence, 1102 suggests that a preoperative platelet count 50 000 µL⁻¹ may be acceptable. Severe thrombocytopenia (50 000 platelets µL⁻¹) occurs in 1% of patients. 1103 Due to an assumed increased bleeding risk, this value is a common trigger for prophylactic preoperative platelet transfusion.

A platelet count 50 000 µL⁻¹ may trigger platelet transfusion in cirrhotic patients during active bleeding 99 and is recommended as a threshold for platelet transfusion before liver biopsy, despite limited supporting evidence. 1099

Thrombocytopenia (<150 000 platelets µL⁻¹) occurs in ≥75% of liver disease patients, 1104 limiting thrombin generation and potentially increasing bleeding risk. 1102

Among liver disease patients undergoing invasive procedures, bleeding occurred in 31% of cases with severe thrombocytopenia, and none of those with moderate


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thrombocytopenia. However, among patients with severe thrombocytopenia, the prevalence of significant coagulopathy did not differ between those who bled and those who did not.

8.4.1.5 Platelet function in cirrhosis

Recommendations

PFA-100 is not predictive of bleeding risk in cirrhosis. C

Bleeding time is influenced by many variables and is not useful to stratify bleeding risk. C

Primary haemostasis may function effectively in cirrhosis, and low platelet count alone might not increase bleeding risk. Primary haemostasis in cirrhosis has been assessed using bleeding time, where bleeding time increased progressively from Child-Pugh class A to class C. However, the validity of prolonged bleeding time as a risk factor for bleeding in cirrhosis remains uncertain. Assessment of bleeding risk using the platelet count has been recommended instead.

Chronic inflammation coupled with increased vWF concentrations may enhance platelet activity in cirrhosis, potentially explaining normal bleeding time measurements in patients with low platelet counts. Alternatively, altered vasoreactivity and/or arterial dysfunction, both well documented in cirrhosis, may explain prolonged bleeding time. PFA-100 closure time is prolonged in cirrhosis, although the prognostic value of this is unknown.

Anaemia may potentially increase bleeding tendency by impairing platelet function; its impact warrants further investigation.

8.4.2 Acute liver failure and invasive procedures

Recommendation

We recommend that, in acute liver failure, moderately elevated INR should not be corrected before invasive procedures, with the exception of intracranial pressure monitor insertion. 1C

Acute liver failure (ALF) is defined by encephalopathy and coagulopathy (INR > 1.5) within 26 weeks of onset of acute liver disease. Severity of coagulopathy is a useful prognostic marker for monitoring hepatic function. A review of >1000 patients with ALF reported a mean INR of 3.8. Patients are therefore assumed to have a bleeding diathesis, although clinically significant bleeding is rare (around 5%) and TEG results are typically normal. Haemostatic alterations in ALF differ from those in CLD. Thrombocytopenia is less common in ALF, pro- and anticoagulant depletion is more severe and fibrinolysis is inhibited due to high PAI-1 concentrations. TEG clot strength is most influenced by platelet count, followed by fibrinogen concentration, then procoagulant factor levels. Prophylactic FFP transfusion to correct INR is not justified in ALF and compromises INR as an indicator of liver function.

Coagulopathy is almost always treated in ALF patients before invasive procedures; however, such practice is not supported by data and there are no evidence-based guidelines recommending an appropriate target INR. Historical consensus suggests a target INR <1.5, although available data challenge this. Transfusion-free OLT has been described in patients with ALF, with INR up to 8, and INR does not predict intraoperative blood loss.

PT and INR can be corrected using rFVIIa, which has been used before intracranial pressure monitor insertion. However, the evidence for rFVIIa efficacy in reducing bleeding complications is limited. Optimal dosing remains uncertain, as does the thrombogenic potential of rFVIIa. Before invasive procedures, fibrinogen concentrations <1 g l⁻¹ should be corrected with cryoprecipitate or fibrinogen concentrate. Platelet count ≥50 000 μL⁻¹ is acceptable and there are no clear guidelines concerning clotting factors. With the exception of intracranial pressure monitor insertion, INR should not be corrected preoperatively.

INR correction with FFP introduces volume overload and haemodilution. Correction of coagulation factor concentrations above 30% requires up to 30 ml kg⁻¹ FFP. Plasma exchange plasmapheresis with FFP may correct INR and improve haemostasis. PCC with vitamin K can rapidly correct markedly elevated PT/INR before urgent invasive procedures. Further, prospective RCTs are required in this area.

8.4.3 Orthotopic liver transplantation

Median transfusion during orthotopic liver transplantation (OLT) has decreased from 20 to 2 U since the 1980s. The procedure is now often performed without transfusion, although massive transfusion is still required occasionally. Coagulopathic bleeding may be related to dilutional coagulopathy or hyperfibrinolysis.

The aetiology of liver failure is an independent parameter for predicting massive blood loss. Fewer bleeding complications are observed in cholestatic liver disease compared with viral or toxic liver disease. Preoperative PT/INR does not predict the need for transfusion, whereas preoperative haemoglobin concentration does.

Practice varies between centres with regard to transfusion thresholds and coagulation monitoring. The number of RBC units transfused intraoperatively shares an inverse relationship with patient survival and guidelines are intended to limit unnecessary transfusion.

8.4.3.1 Methods to reduce blood loss in liver transplantation

Both RBC and platelet transfusion independently predict poor outcome in OLT. Approaches to minimising
transfusion include normothermia, because hypothermia reduces platelet function and impairs coagulation enzyme activity. Even mild hypothermia (<35.5 °C) increases blood loss by 16% and the relative risk of transfusion by 22%.486

8.4.3.2 Intraoperative fluid management

Recommendation
Fluid restriction, phlebotomy, vasopressors and transfusion protocols may be associated with low transfusion rates during OLT. C

In cirrhotic patients, volume loading only marginally increases cardiac output while portal hyperaemia and bleeding are increased. Low transfusion rates (<80%) during OLT have been reported using fluid restriction, phlebotomy, vasopressors and transfusion protocols.1128,1129 However, aggressive volume restriction may increase renal dysfunction, limiting its use in some patients.1130

When using colloids, third-generation starch solutions are recommended because they have less effect on coagulation and reduce blood loss and transfusion compared with second-generation starches.863 Patients with end-stage liver disease may exhibit delayed clot formation and reduced clot firmness following even moderate fluid dilution.1131

Thrombin generation in OLT patients is usually normal or supranormal,1086 supporting restrictive FFP transfusion during OLT. If massive bleeding is not evident, FFP transfusion may increase bleeding due to portal hyperaemia.1097

8.4.3.3 Intraoperative cell salvage

Intraoperative cell salvage (ICS) has been used to reduce autologous transfusion requirements and provide cost savings for over two decades.1132 As OLT often involves minimal RBC transfusion, a full ICS setup is not always justifiable. Thus, it is recommended that a ‘stand by’ setup is available. Washed erythrocytes lack clotting factors and platelets, so transfusion therapy must be tailored accordingly. Heparin anticoagulation of salvaged blood appears safe because washed cells contain minimal heparin. Alternatively, citrate may be used.

UK guidelines1133 state that ICS may be considered for hepatocellular tumour surgery if there is a significant risk of major bleeding. Risk of malignant cell reinfusion should be balanced against risk of alloimmune transfusion-related complications. Leukodepletion filters reduce reinfusion risks1134 but also reduce reinfusion speed. OLT studies have not shown any risk of bacterial contamination. During ICS, blood should be collected only after ascitic fluid has been removed and should cease once biliary anastomosis begins.

8.4.4 Coagulation monitoring

Differences between centres in coagulation monitoring contribute to variations in OLT transfusion practice.1135 Laboratory-based coagulation tests are unsuitable because of slow turnaround times and inability to diagnose hyperfibrinolysis.1135

8.4.4.1 Global coagulation tests: thrombelastography (TEG)/thromboelastometry (ROTEM)

Recommendation
We recommend the use of perioperative coagulation monitoring using ROTEM/TEG for targeted management of coagulopathy. 1C

TEG monitoring can reduce transfusion requirements by 30%.1136,1137 However, high quality data supporting the effectiveness of such practice is lacking.1138 In a Cochrane review of TEG/ROTEM haemostatic monitoring,17 only one RCT related to liver transplantation133 and this was not blinded. Other evidence suggests TEG/ROTEM monitoring may help reduce bleeding and transfusion of FFP and platelets in liver transplantation.1139 As RBC and platelet transfusions are associated with increased mortality, TEG/ROTEM could help to improve patient outcomes; however, larger trials are required to investigate this.1139,1127

TEG/ROTEM can facilitate targeted management of specific coagulopathies, potentially reducing transfusion requirements.134,1113 Diagnostic capability is maximised using different activators and modifiers (described elsewhere in this guideline – see section 4.2.3.2). TEG/ROTEM can identify hyperfibrinolysis, indicating antifibrinolytic therapy.1140 In addition, the FIBTEM test can guide administration of fibrinogen concentrate or cryoprecipitate,1058 in turn reducing platelet and RBC transfusions.1141

A heparin effect is commonly evident during reperfusion, due to heparin administered to the donor and endogenous vascular endothelial heparinoids.1140 Reversal with protamine is rarely indicated because the effects of the heparin are temporary and do not usually increase bleeding risk.1142

8.4.5 Pharmacological therapy

8.4.5.1 Antifibrinolytic drugs

Recommendation
Antifibrinolytic therapy reduces blood loss and transfusion requirements in liver transplantation. B

We recommend antifibrinolytic drugs for treatment of fibrinolysis (evident from microvascular oozing or TEG/ROTEM clot lysis measurement) and not for routine prophylaxis. Marginal grafts (e.g. donation after cardiac death) increase the risk of fibrinolysis following reperfusion. 1C
Lack of tissue plasminogen activator (tPA) clearance increases fibrinolysis during OLT. Dramatically elevated levels of tPA follow reperfusion, causing explosive primary hyperfibrinolysis and, potentially, diffuse bleeding. Hyperfibrinolysis typically subsides within an hour but may persist with poorly functional or marginal grafts. This scenario rarely occurs in ALF due to elevated PAI-1. Antifibrinolytic drugs have been used prophylactically and therapeutically for TEG-determined fibrinolysis.  

A Cochrane review demonstrated that antifibrinolytic therapy helps to reduce blood loss and perioperative allogeneic blood transfusion. Tranexamic acid and EACA were generally as effective as aprotinin. Aprotinin was not associated with increased risk of vascular occlusion and death, but an increased risk of renal failure could not be excluded. An observational study involving OLT patients found a significant risk of transient renal dysfunction with aprotinin, but no increase in renal failure or mortality. A meta-analysis of antifibrinolytic drugs concluded that both aprotinin and tranexamic acid reduce RBC transfusion in OLT. Aprotinin, but not tranexamic acid, also reduces intraoperative FFP transfusion. There was no evidence of antifibrinolytic therapy increasing risks of hepatic artery thrombosis, venous thromboembolism or mortality. Similarly, a review of over 1400 OLT patients found no difference in arterial or venous thromboembolism between patients receiving aprotinin and no treatment. However, this does not preclude risks in specific patient subgroups or with specific doses. EACA is widely used in the USA despite the existence of only one RCT, and this study demonstrated no benefit versus placebo.  

As massive bleeding has become less frequent during OLT, there have been moves from routine to selective antifibrinolytic prophylaxis (high-risk patients), and onto treatment only. Predicting hyperfibrinolysis is problematic because bleeding is greatly influenced by the donor liver, which is not reflected in preoperative assessment. Treatment using tranexamic acid/EACA is recommended if microvascular oozing or fibrinolysis is evident. Timing and degree of fibrinolysis is important; non-severe fibrinolysis occurring after reperfusion may resolve spontaneously. Lowest effective doses are uncertain; tranexamic acid is currently given in 1–2 g increments.  

**Recombinant activated factor VII**  
**Recommendation**  
*We recommend against rFVIIa for prophylaxis; rFVIIa should be used only as rescue therapy for uncontrolled bleeding.*  

Two RCTs have investigated prophylactic rFVIIa in OLT, both demonstrated correction of INR but no reduction in transfusion. Off-label ‘rescue’ therapy with rFVIIa may help to control haemorrhage. However, systematic reviews show no reduction in mortality and increased risk of arterial thromboembolism.  

**8.4.6 Pulmonary emboli and intracardiac thrombi in orthotopic liver transplantation**  
Perioperative intracardiac and pulmonary emboli are rare but potentially lethal complications of OLT. A systematic review reported an incidence of 1% and mortality of 68%. The aetiology is uncertain but unlikely to be causally related to venovenous bypass or antifibrinolitics. One study described a 1.9% incidence of intracardiac thrombi (ICT), mostly in association with reperfusion. Portal hypertension and intraoperative haemodilution were independent risk factors. Routine intraoperative transoesophageal monitoring is recommended to identify ICT. ICT has been linked with hypercoagulability according to TEG, even when conventional tests suggest hypocoagulability. In addition, the value of thromboelastometry was demonstrated in a fatal cardiopulmonary embolism following aprotinin therapy.  

Postoperative LMWH prophylaxis for thromboembolic complications is not administered universally. However, accumulating evidence supports LMWH prophylaxis and extended postoperative coagulation monitoring.  

**8.4.7 Antiplatelet therapy and platelet function testing**  
**Recommendation**  
*POC platelet function tests may help to stratify risk and rationalise platelet transfusion in patients taking antiplatelet drugs.*  

A small number of OLT patients receive antiplatelet therapy for prevention of coronary/cerebral vascular disease or for coronary stent insertion. An observational study involving coronary stented patients undergoing cardiac surgery reported that although the risks of major bleeding decreased, the risk of major adverse cardiac and cerebrovascular events increased if antiplatelet therapy was interrupted for more than 5 days preoperatively. In emergency surgery or OLT, prior therapeutic interruption is not feasible.  

The degree of platelet inhibition is variable; ‘hyper-responders’ may be at increased risk of ischaemic events, while ‘hyper-responders’ may have increased risk of bleeding. Bleeding risk may be stratified using point-of-care platelet function analysers: minimal risk is associated with platelet inhibition <30%, but >60% inhibition with 2- to 6-fold increased risk. Cardiac surgery patients with high platelet inhibition appear to have increased bleeding risk and increased transfusion requirements. Patients in the lower tertile of platelet aggregation (measured using multiple electrode aggregometry) receive more platelet concentrate than upper
tertile patients. Similarly, the m-TEG platelet mapping assay (Haemonetics, Braintree, MA) has shown that >70% inhibition increases bleeding risk. Platelet mapping has been used to guide antplatelet therapy in a Budd-Chiari patient with an occluded transjugular intrahepatic portosystemic shunt. Tranexamic acid may partially reverse the effect of antplatelet therapy.

Platelet function tests may potentially predict platelet transfusion requirements although no ‘gold standard’ test or cut-off value has yet been established. Studies are ongoing.

8.4.8 Liver resection
Blood loss during liver resection is a major determinant of perioperative outcome. Selective vascular occlusion techniques help to control blood loss, with complete vascular occlusion employed in excessive bleeding. Intermittent clamping or ischaemic preconditioning may reduce ischaemic liver injury.

8.4.8.1 Haemodynamic interventions to reduce blood loss
Recommendation
A low central venous pressure and restrictive fluid administration reduce bleeding. B

Fluid restriction and maintenance of low central venous pressure (CVP) during hepatic resection reduce blood loss. However, low CVP may increase complications including air embolism and renal failure. It is uncertain whether fluid restriction during hepatic resection increases the risk of renal dysfunction, although this risk is generally considered minimal.

8.4.8.2 Pharmacological interventions to reduce blood loss
Recommendation
We suggest that antifibrinolytic drugs should be considered in cirrhotic patients undergoing liver resection. 2C

A Cochrane review reported reduced allogeneic transfusion in patients receiving aprotinin or tranexamic acid. Desmopressin, rFVIIa and AT did not decrease transfusion. However, because all of the studies had a high risk of bias (likely type I and type II errors), no general recommendations can be made without further large trials. A separate systematic review showed no difference between rFVIIa and placebo.

8.4.9 Acute upper gastrointestinal bleeding
In decompensated CLD, bleeding is often triggered by haemodynamic alterations arising from portal hypertension, endothelial dysfunction, renal failure, bacterial infection, endogenous heparinoids and DIC. Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency, with a mortality in excess of 7%.

8.4.9.1 Acute variceal bleeding
Recommendations
We recommend that acute variceal bleeding should be managed by a multidisciplinary team. A specific multimodal protocol for upper gastrointestinal haemorrhage should be available. 1C

We recommend that early treatment involves immediate use of vasopressors (somatostatin or terlipressin) to reduce bleeding and early interventional endoscopy. Antibiotics must be started on admission. 1A

Variceal bleeding is a major complication of portal hypertension and a leading cause of death in cirrhosis. Although management and prognosis have improved, early mortality following acute variceal bleeding (AVB) remains high (15–24%). AVB outcomes can be improved by experienced multidisciplinary management and immediate interventional endoscopy. Early risk assessment (Rockall scoring system or Blatchford score) is important. Combined pharmacological and endoscopic intervention is recommended for initial treatment of acute bleeding. Vasoactive drugs (preferably somatostatin or terlipressin) may improve control of haemorrhage and should be given immediately if variceal bleeding is suspected, with maintenance for 2–5 days.

Following stabilisation with fluid and blood support, emergency diagnostic endoscopy and endoscopic variceal treatment should be performed by a skilled endoscopist. Antibiotic prophylaxis forms an integral component of AVB treatment, commencing at admission and maintained for ≥7 days. For acute refractory bleeding, rescue therapy should begin immediately. Balloon tamponade may be necessary and shunt therapies are often effective if initial treatment fails.

8.4.9.2 Fluid Resuscitation and pharmacological interventions
Recommendations
Tranexamic acid reduces mortality but not rebleeding. B rFVIIa should be used only as rescue therapy; we recommend against its routine use. 1C

Blood volume resuscitation should be undertaken as soon as possible with the aim of maintaining systolic blood pressure at around 100 mmHg. Optimal volume replacement remains controversial. No high-quality RCTs have compared crystalloids with colloids in patients with UGIB; however, in critical care, a meta-analysis and a large RCT suggest no differences between them. Conservative volume replacement and transfusion is recommended. Because colloids remain intravascular for longer and reduce the total administration volume, they may be preferable. Vasoactive drugs have been shown to counteract portal pressure increases induced by volume expansion.


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Blood transfusion should generally aim to maintain haemoglobin at 7–8 g dl\(^{-1}\). Abnormal PT/INR and platelet count correlate poorly with bleeding and TEG may provide more useful information\(^{1.175,1176}\). In active bleeding, FFP should be given to maintain INR < 2 and platelets given to maintain platelet count >60 000\(\mu\)l\(^{-1}\).\(^{1.1402}\) The value of antifibrinolytic drugs in treating UGIB is unclear. Meta-analyses suggest that tranexamic acid does not lower rates of rebleeding or surgery, but that it reduces mortality (relative risk 0.61).\(^{1.175,1178}\) large RCTs are needed to confirm these findings.

PT can be corrected using rFVIIa in CLD patients with UBIG. Benefits over standard therapy are not evident, although a possible indication exists in uncontrolled bleeding.\(^{1.1180}\) European guidelines on rFVIIa recommend against its use in elective liver surgery or bleeding episodes in patients with Child-Pugh A cirrhosis. Efficacy in Child-Pugh B and C is uncertain and thromboembolic events remain a concern.\(^{1.1181}\)

### 8.4.10 Coagulopathy and renal disease

Patients with chronic kidney disease (CKD) have haemostatic derangement with variable clinical manifestations.\(^{1.1182}\) As CKD advances, procoagulant abnormalities (impaired tPA release, increased PAI-1, elevated fibrinogen and increased TF/FVIII) persist.\(^{1.1183}\) Patients also develop platelet dysfunction, comprising impaired GPIIb/IIIa receptor function, altered release of ADP and serotonin from platelet granules, and faulty arachidonic acid and prostacyclin metabolism.\(^{1.1184}\) Uraemic toxins may stimulate nitric oxide release, exacerbating platelet dysfunction. Correction of anaemia in CKD patients may improve platelet function.\(^{1.1185}\)

#### 8.4.10.1 Assessment of platelet function in chronic kidney disease

**Recommendation**

*Point-of-care tests of platelet function and bleeding time provide no reliable platelet function assessment in uraemia and no prediction of bleeding in this setting. C*

CKD patients typically have normal/slightly reduced platelet counts. Skin bleeding time (SBT) has been used to assess platelet function, but this has poor reproducibility. The PFA-100 has better sensitivity and specificity than SBT.\(^{1.1186}\) However, correlation has not been shown between PFA-100 closure times and bleeding complications after percutaneous renal biopsy.\(^{1.1187}\) A review of point-of-care platelet function tests found inconsistent results, so the authors could not recommend any single test for bleeding risk assessment.\(^{1.1188}\)

#### 8.4.10.2 Correction of bleeding diathesis and treatment of bleeding in patients with renal failure

**Recommendations**

We suggest that conjugated oestrogen therapy should be used in uraemia. 2C

We suggest that desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. 2C

There is no evidence to support use of rFVIIa in this setting.

Bleeding complications are common in acute and chronic renal failure.\(^{1.1189}\) Modern dialysis techniques, combined with correction of anaemia using erythropoietin, have reduced spontaneous haemorrhage, although bleeding diathesis remains a problem in uraemic patients undergoing invasive/surgical procedures. Several measures are available to reduce bleeding risk in advanced CKD patients:

1. Renal replacement therapy (peritoneal dialysis or haemodialysis) improves platelet function by removing uraemic toxins.\(^{1.1185}\)
2. Correction of anaemia in CKD with erythropoietin helps to prevent uraemic bleeding. Increased erythrocyte numbers improve platelet function, and decreased haemoglobin concentration may intensify platelet dysfunction.\(^{1.1190}\)
3. Desmopressin can treat platelet dysfunction in uraemic patients. Desmopressin induces VWF release, improving platelet adhesion/aggregation. Desmopressin shortens bleeding time within 1 h, with effects lasting 4–8 h, and a single dose of 0.3 mg kg\(^{-1}\), intravenously or subcutaneously, is effective. Doses of 3 mg kg\(^{-1}\) can also be administered nasally. Desmopressin is effective as both prophylaxis and treatment of perioperative bleeding.\(^{1.1193,1194}\)
4. Cryoprecipitate has been used to treat uraemic bleeding. It is effective 1 h after infusion, with maximum effect after 4–12 h. Up to 50% of uraemic patients fail to respond to cryoprecipitate. Cryoprecipitate carries a risk of pathogen transmission and is rarely used in CKD.\(^{1.1182}\)
5. Conjugated oestrogens may reduce bleeding in uraemic patients, particularly those with gastrointestinal or intracranial bleeding or undergoing major surgery. An oral dose of 25 mg normalises SBT for 3–10 days.\(^{1.1196}\) Low dose transdermal oestrogen (oestradiol 50–100 µg per day) reduces gastrointestinal bleeding and improves bleeding time.\(^{1.1197}\)
6. Tranexamic acid shortens bleeding time in uraemic patients. However, it may accumulate in patients with renal insufficiency and there is no evidence of superiority over other therapies. Therefore, tranexamic acid should be considered only in the acute setting when other treatments have proved unsatisfactory.\(^{1.1185}\)
7. Anecdotal reports suggest that rFVIIa may control bleeding in uraemic patients. However, there are no data supporting its safety, efficacy or dosing in this setting.


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8.5 Paediatric surgery

8.5.1 Introduction
Severe perioperative bleeding in paediatric patients has typically been treated as it is in adults. Despite developmental changes in the coagulation system, haemostatic capacity is excellent in newborns and children. Nonetheless, recognition of these developmental changes may improve the management of acquired paediatric coagulopathy.

8.5.2 Coagulation monitoring
Recommendation
We suggest the use of perioperative coagulation analysis using viscoelastic point-of-care monitoring (ROTEM/TEG) for timely detection of coagulation defects including dilutional coagulopathy and hyperfibrinolysis.

Diagnosing paediatric perioperative coagulopathy requires rapid, robust coagulation monitoring, alongside age-specific reference ranges. ROTEM and TEG can complement standard coagulation tests, especially in the perioperative setting. In a meta-analysis, TEG or ROTEM-guided transfusion was shown not to affect overall mortality in patients with severe bleeding, but it was associated with significantly reduced bleeding. Data supporting the effectiveness of ROTEM/TEG-guided paediatric coagulation therapy are limited.

8.5.3 Fluid resuscitation
Recommendation
No clear recommendation can be made regarding the choice of perioperative fluid replacement in children.

Despite age-dependent variations in coagulation factor levels, the pathophysiology underlying paediatric perioperative bleeding is comparable to adults. Dilutional coagulopathy is encountered in adults and children alike. However, a negative impact of colloids on haemostasis should be considered and closely monitored. Cardiopulmonary bypass may cause additional haemostatic disturbances, including platelet dysfunction and excessive fibrinolysis.

Fluid resuscitation can cause dilutional coagulopathy. Pronounced coagulation disturbance following HES infusion and minor disturbances following gelatin solution or albumin have been reported. A meta-analysis suggests that colloids are no more effective than crystalloids for reducing mortality in critically ill adults. Together, no clear recommendation can be made regarding choice of fluid for paediatric perioperative resuscitation.

8.5.4 Red blood cell transfusion
Recommendation
We suggest that a critical haemoglobin threshold of $8 \text{ g dl}^{-1}$ for RBC transfusion may be safe in severe paediatric perioperative bleeding.

Haemoglobin concentrations vary with age and gender, and RBC transfusion should be tailored accordingly. The required transfusion volume can be calculated as: body weight (kg) x desired increment in haemoglobin concentration (g dl$^{-1}$) x 5. In massive bleeding, haemoglobin concentrations should be maintained at $\geq 8 \text{ g dl}^{-1}$ while in stable, critically ill children, $7 \text{ g dl}^{-1}$ may suffice.

8.5.5 Platelet transfusion
Recommendation
We suggest that transfusion of platelet concentrates may be considered if platelet count is $< 50 000–100 000 \text{ µl}^{-1}$.

In children and adults, transfusion thresholds for platelets vary according to the type of surgery and platelet functionality. Current data suggest maintaining platelet count at $\geq 50 000–100 000 \text{ µl}^{-1}$. Transfusion of one unit of platelet concentrate per 10 kg body weight, or 5 ml kg$^{-1}$ of apheresis platelet concentrate, should raise platelet count by 20 000–50 000 µl$^{-1}$.

8.5.6 Fresh frozen plasma
Recommendation
No clear recommendation can be made regarding the indication and dosing of FFP transfusion in bleeding children, but severe risks have been reported.

Transfusion of FFP for treatment of severe bleeding is recommended by several guidelines but is not supported by high quality evidence.

No randomised, controlled trials have demonstrated that FFP controls paediatric perioperative bleeding. Prophylactic FFP in preterm babies appears not to reduce mortality or disability associated with haemorrhagic/ischaemic brain injury. Intraoperative FFP transfusion during paediatric craniofacial surgery may not reduce RBC transfusion or blood loss compared with albumin, although other results do suggest improved postoperative coagulation.

UK guidelines recommend avoiding FFP for simple volume replacement and one UK study questioned the overall clinical benefits of FFP. Guidelines typically recommend 10–15 ml kg$^{-1}$ FFP for adults and children with acquired bleeding and prolonged aPTT or PT (> 1.5 times normal) However, this may be insufficient to achieve haemostasis and the potential for volume overload may preclude increased dosing. Side-effects of FFP include TRALI and an increased mortality in children.
with ALI, transfusion-associated cardiac overload, sepsis in severely burned paediatric patients, transfusion-related immunomodulation and multiple organ failure.

8.5.7 Coagulation factor concentrates

Coagulation factor concentrate therapy for congenital disorders has established the potential for paediatric coagulation factor concentrate therapy in acquired perioperative coagulopathies. However, there is a lack of randomised, controlled trial data in children.

8.5.7.1 Fibrinogen concentrate

Recommendations

We suggest that fibrinogen concentrate (30–50 mg kg\(^{-1}\)) or cryoprecipitate (5 ml kg\(^{-1}\)) may be used to increase plasma fibrinogen concentrations above trigger values of 1.5–2.0 g l\(^{-1}\) or FIBTEM MCF > 7 mm in bleeding children.

We suggest that FFP may be used if no other fibrinogen source is available.

Fibrinogen is the first clotting factor to reach critically low concentrations during life-threatening haemorrhage in adults and children. European guidelines recommend higher thresholds (1.5–2.0 g l\(^{-1}\)) than international guidelines. Fibrinogen substitution can be performed using cryoprecipitate (5 ml kg\(^{-1}\)), but this is not available in all countries due to safety concerns. FFP may not provide an adequate increase in plasma fibrinogen concentrations. In contrast, fibrinogen concentrate (30 mg kg\(^{-1}\)) has been used effectively to treat fibrinogen deficiency during paediatric craniofacial surgery. This is supported by evidence from prospective adult studies demonstrating the effectiveness of fibrinogen concentrate in aortic surgery, radical cystectomy and major orthopaedic surgery.

Fibrinogen concentrate has a favourable safety profile.

8.5.7.2 Prothrombin complex concentrate

Recommendation

Data for PCC in children are limited and no dose recommendation can be made.

PCC can help to correct dilutional coagulopathy by increasing thrombin generation. In adults, 20–30 IU kg\(^{-1}\) PCC should be sufficient to increase thrombin potential, but there is no evidence on the safety, effectiveness or optimal dosing of PCC for paediatric perioperative bleeding.

8.5.7.3 Coagulation factor XIII

Recommendation

No recommendation on the use of FXIII concentrate in bleeding children can be made.

Acquired FXIII deficiency appears prevalent in surgical and acute care settings. A randomised trial in adults, together with other investigations, suggest maintaining FXIII levels above 50–60% of normal during perioperative bleeding. FXIII may be supplemented using FXIII concentrate (20 IU kg\(^{-1}\)) or FFP transfusion. No data exist on paediatric FXIII supplementation.

8.5.7.4 Recombinant activated factor VII

Recommendation

We recommend against the use of rFVIIa in children.

rFVIIa has been described as useful for controlling severe bleeding in cardiac and neurosurgical procedures in children, although a prospective, randomised trial in paediatric cardiac surgery showed no difference in blood loss with rFVIIa versus placebo. Failure of rFVIIa to reduce RBC transfusion requirements has been reported in adult trauma patients. Undirected rFVIIa administration may potentially increase thromboembolic complications.

8.5.7.5 Desmopressin

Recommendation

We suggest against the routine use of desmospressin in the absence of mild haemophilia A or von Willebrand disease.

Desmopressin has been shown to provide modest reductions in postoperative blood loss and transfusion requirements, without influencing mortality. Maximum effects are observed at a dose of 0.3 μg kg\(^{-1}\). However, paediatric studies in cardiac surgery and other surgical settings have shown no reduction in allogeneic blood transfusion after desmopressin administration.

8.5.7.6 Antifibrinolytics

Recommendation

We suggest that perioperative antifibrinolytic therapy should be used to reduce blood loss and transfusion requirements in cardiac and non-cardiac paediatric surgery.

In paediatric patients undergoing cardiac and scoliosis surgery with high bleeding risk, tranexamic acid markedly reduced perioperative blood loss and RBC transfusion. Similar effects have been reported for tranexamic acid in paediatric craniosynostosis surgery. Optimal dosage remains uncertain, with wide variations in reported loading doses (10–100 mg kg\(^{-1}\)) and infusion rates (1–10 mg kg\(^{-1}\) h\(^{-1}\)). In paediatric cardiac surgery, repeated doses are suggested to be more efficacious than a single bolus.
9 ANTICOAGULATION AND ANTIPLATELET THERAPY

9.1 Introduction
Antithrombotic therapies have a range of indications and in this section we describe how they are used in anaesthesia and intensive care.

9.2 Antiplatelet agents
Perioperative interruption and maintenance of antiplatelet agents (APAs) are associated with increased cardiovascular or haemorrhagic complications, respectively. Guidelines for perioperative APA therapy are based on small observational studies, case reports and expert opinion, so recommendations are weak. In patients with coronary stents, the main risk factor for stent thrombosis is interruption of APA. If these patients require surgery, the optimum delay between stent implantation and surgery is unclear, as is the need for (or optimal duration of) interruption of APA therapy.

9.2.1 Aspirin
Aspirin and other NSAIDs inhibit platelets by inactivating platelet cyclooxygenase-1 (COX-1). Although the effect is irreversible, NSAIDs are weak antiplatelet drugs because they affect only one of the many platelet activation pathways. Randomised trials have shown that aspirin is effective at doses of 50–100 mg per day. There is no convincing evidence that doses >325 mg per day are more effective in reducing the risk of serious vascular events, and higher doses may increase the risk of adverse events (e.g. thrombotic or gastrointestinal). Peak plasma aspirin concentrations occur 30–40 min after ingestion (or 3–4 h for enteric coated aspirin). Platelet function is inhibited within 1 h. The half-life of aspirin is 15–20 min, although platelet inhibition lasts for the lifespan of affected platelets.

Aspirin is indicated and effective for secondary prevention of vascular events. Long-term aspirin therapy reduces the risk of myocardial infarction, stroke or vascular death among high-risk patients (e.g. those with chronic stable angina, prior myocardial infarction, unstable angina, transient ischaemic attack or minor stroke). In such patients, a major vascular event is avoided in 3–5% of individuals over 30 months.

Recommendations
We recommend that aspirin therapy should continue perioperatively in most surgical settings, especially cardiac surgery. Where aspirin withdrawal is considered, we recommend a time interval of 5 days.

Treatment discontinuation increases thrombotic risk; this risk should always be discussed. Following aspirin withdrawal, aspirin treatment should resume as soon as possible postoperatively to prevent platelet activation.

The first postoperative aspirin should be a loading dose, given no later than 24 h after skin closure.

Platelet aggregation is restored approximately 4 days after aspirin discontinuation. Point-of-care testing has demonstrated significant recovery of platelet aggregation within 48 h after aspirin cessation, with baseline values re-established within 5 days. Experimental studies have reported enhanced platelet aggregation after interruption of aspirin. Platelet thrombi produced after aspirin withdrawal appear more resistant to physiological fibrinolysis. Aspirin or antiplatelet withdrawal has been linked to myocardial infarction or stroke.

In a cohort of acute coronary syndrome (ACS) patients, Collet et al. reported ACS to be associated with aspirin interruption in 5.4% of patients. Ischaemic events were typically observed 12 days after aspirin withdrawal. Other reports associate aspirin interruption with thrombotic events in patients with a history of coronary heart disease, stroke and peripheral artery disease.

Surgical bleeding risk associated with APA therapy has been poorly evaluated. In patients undergoing total hip replacement, preoperative aspirin was associated with only a minor increase in bleeding compared with placebo (Pulmonary Embolism Prevention [PEP] trial). Systematic reviews have analysed aspirin-associated bleeding risks in non-cardiac surgery. Burger et al. pooled data from 49 590 patients (14 981 on aspirin). Aspirin increased the rate of bleeding complications 1.5-fold but did not increase their severity (except in intracranial surgery and possibly transurethral prostatectomy). Giannarini et al. showed that continued low-dose aspirin (100 mg per day) in men undergoing transrectal prostate biopsy did not increase the incidence of mild bleeding, although the durations of self-limiting haematuria and rectal bleeding were prolonged.

In patients referred for transurethral prostatectomy, open prostatectomy and transurethral resection of bladder tumour, postoperative bleeding did not differ significantly between patients in whom aspirin was initiated early (24 h) or late (3 weeks) after surgery. Several other articles report similar findings. In general, aspirin should not be withdrawn perioperatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug. Aspirin is administered preoperatively for most vascular procedures. The Eighth ACCP Guidelines strongly recommend aspirin for carotid endarterectomy; aspirin, 75–325 mg per day should be given preoperatively and continued indefinitely (grade of recommendation: 1A). Two studies have since been published. Oscarsson et al. conducted a randomised, double-blind, placebo-controlled trial to compare the effect of low-dose aspirin with that of placebo on myocardial damage, cardiovascular and bleeding complications in high-risk patients undergoing non-cardiac surgery.
Aspirin (75 mg) or placebo was given 7 days before surgery and continued until the third postoperative day. One hundred and nine of the patients received aspirin and 111 received placebo. Treatment with aspirin resulted in a 7.2% absolute risk reduction (95% CI, 1.3–13%) for postoperative major adverse cardiovascular events (MACE). The relative risk reduction was 80% (95% CI, 9.2–95%). No significant differences in bleeding complications were seen between the two groups. The STRATAGEM study was a randomised, multicentre, blinded study in which 145 patients in the aspirin group were treated for 10 days preoperatively, and 146 patients were in the placebo group. No significant difference was observed in either the primary outcome score, or at day 30, in the number of major complications between groups. In addition, no difference in major bleeding was observed. In summary, these studies showed that there was no risk in continuing aspirin perioperatively.

**Recommendation**

For intra- or postoperative bleeding clearly related to aspirin, we suggest that platelet transfusion be considered (dose: 0.7 × 10^11 [i.e. two standard concentrates] per 7 kg body weight in adults). 2C

Severe bleeding in patients on aspirin may require immediate platelet transfusion. 1075

### 9.2.2 Thienopyridines: clopidogrel and prasugrel

The thienopyridine derivatives ticlopidine and clopidogrel inhibit ADP-induced platelet activation by binding covalently to the P2Y12 receptor. These agents are more potent than aspirin, although platelet activation remains possible with high concentrations of agonists acting through phospholipase C.

Clopidogrel is absorbed rapidly and metabolised extensively. The main systemic metabolite is the carboxylic acid derivative SR 26334. The plasma elimination half-life of SR 26334 is approximately 8 h. 1254

Prasugrel is a new thienopyridine agent and a highly potent APA. It requires conversion to an active metabolite before binding to the platelet P2Y12 receptor, and its antiplatelet activity is more rapid, consistent and pronounced than that of clopidogrel. 1254 It is rapidly absorbed and the hepatic CYP system converts it into the active form. The active metabolite concentration peaks 30 min after administration and has an elimination half-life of approximately 3.7 h. Differences in metabolic processing result in higher concentrations of active metabolite and therefore improved inhibition of platelet aggregation with prasugrel compared with clopidogrel. 1254 No data are available regarding perioperative use of prasugrel. Its antiplatelet effect lasts for the platelet’s lifespan (≥7 days). Recommendations for clopidogrel should be applicable to prasugrel, except for the duration of withdrawal (no more than 7 days for prasugrel).

**Recommendations**

*Clopidogrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 5 days.* 1C

*Prasugrel increases perioperative bleeding. In cases of increased bleeding risk, we recommend that it should be withdrawn for no more than 7 days.* 1C

We recommend that antiplatelet agent therapy should resume as soon as possible postoperatively to prevent platelet activation. 1C

We suggest that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure. We also suggest that this first dose should not be a loading dose. 2C

Several publications have described perioperative haemorrhagic complications associated with clopidogrel, and the risk may increase when clopidogrel is combined with aspirin. However, such risks may be acceptable if withdrawal is also associated with a high risk of thrombotic complications.

A study of clopidogrel in healthy volunteers showed high interindividual variability in platelet inhibition during treatment and recovery of platelet function after discontinuation. This may be explained in part by genetic polymorphism of CYP450 involved in the metabolism of clopidogrel. A low level of inhibition of platelet aggregation may be associated with an increased incidence of cardiac events, but no evidence was identified establishing a relationship between clopidogrel platelet inhibition and bleeding.

In a porcine study, clopidogrel prolonged ear-immersion bleeding time more than did aspirin. 1256 However, no clinical comparison of aspirin and clopidogrel has been performed in surgical patients.

**Recommendation**

*We recommend postponement of elective surgery following coronary stenting (at least 6 to 12 weeks for bare metal stent and one year for drug-eluting stents).* 1C

Kaluza et al. 1269 reported that surgery performed within 4 weeks after insertion of a bare metal stent (BMS) is associated with 20% mortality, caused either by ischemic events following APA interruption or haemorrhagic events while APA therapy was maintained. Other studies confirm that the first month following BMS placement is a high-risk period for non-cardiac surgery. Nuttall et al. 1270 reported a postoperative cardiac event rate of 10.5% for surgery within 1 month after stent insertion, versus 3.8% between 1 and 3 months, and 2.8% after 90 days. A global consensus statement recommends...
avoidance of non-emergency non-cardiac surgery during the first 4–6 weeks following BMS placement.

**Recommendations**

We recommend that a multidisciplinary team meeting should decide on the perioperative use of antiplatelet agents in urgent and semi-urgent surgery. 1C

We suggest that urgent or semi-urgent surgery should be performed under aspirin/clopidogrel or aspirin/prasugrel combination therapy if possible, or at least under aspirin alone. 2C

Clopidogrel is approved for reduction of atherosclerotic events following recent stroke, recent myocardial infarction or established peripheral arterial disease. The clinical benefit of clopidogrel and aspirin, versus aspirin alone, has been confirmed in patients experiencing percutaneous coronary intervention (PCI) or acute myocardial infarction. The benefit of dual antiplatelet therapy versus aspirin alone in patients with ACS is around one-third of the benefit of aspirin versus no antiplatelet therapy. In the future, prasugrel may be used similarly to clopidogrel, but currently, prasugrel is ‘co-administered with acetylsalicylic acid for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI’. A large phase III study (TRITON) compared prasugrel with clopidogrel in 13 608 patients with ACS scheduled to undergo PCI. Prasugrel reduced rates of ischaemic events including stent thrombosis, but increased the risk of major/fatal bleeding.886

Drug-eluting stents (DESs) have been associated with stent thromboses at a rate of 1% per year.1271 Mortality for this complication is 40–50% and the major risk factor for stent thrombosis may be APA withdrawal.1272 Eisenberg et al.1273 identified 161 cases of late or very late stent thrombosis; 19 cases occurred in patients receiving dual antiplatelet therapy at the time of the event. The median time to event was 7 days if both APAs were stopped simultaneously, 7 days if a thienopyridine was withdrawn first with no ill effect and aspirin subsequently stopped, and 122 days if the thienopyridine was removed but acetylsalicylic acid was maintained. Maintaining APAs throughout the procedure appears to be the safest approach. Among DES patients undergoing non-cardiac surgery, the period of risk for major cardiac events seems to be 1 year.1274 The incidence of perioperative stent thrombosis remains controversial. Godet et al.1275 reported two stent thromboses in 96 DES patients undergoing non-cardiac surgery, while Schouten et al.1276 observed three late stent thromboses in 99 DES patients undergoing invasive procedures. The risk of stent thrombosis seems to increase over 50-fold during the perioperative period, compared with the annual cumulative risk (0.5–1.5%). Finally, Albaladejo et al.1158 observed major postoperative cardiovascular complications in 10.9% of coronary stent patients undergoing non-cardiac surgery. Preoperative risk factors were anaemia, severe renal failure, urgent surgery, high-risk surgery and interruption of antiplatelet treatment for more than 5 days preoperatively.

The Triton TIMI 38 study showed increased haemorrhagic complications in CABG patients treated with dual antiplatelet therapy including prasugrel, compared with patients treated with clopidogrel.886

**Recommendation**

We suggest that platelet transfusion should be considered (dose: 0.7 x 10^11 [i.e. two standard concentrates] per 7 kg body weight in adults) in cases of intra- or postoperative bleeding clearly related to clopidogrel or prasugrel. 2C

No studies of platelet transfusion for reversal of clopidogrel or prasugrel treatment were retrieved.

9.2.3 Ticagrelor

In contrast to the thienopyridines, ticagrelor acts directly on the P2Y12 receptor rather than requiring cytochrome P450 biotransformation. Metabolites of ticagrelor are also active.1277 Like prasugrel, ticagrelor provides faster (<2 h), greater (approximately 70%) and more consistent P2Y12 inhibition than does clopidogrel (30–40%). Ticagrelor has a rapid onset of action, reversible binding and relatively short duration of action (48–72 h), necessitating twice-daily oral administration. The half-life of the active compound is 12 h. Following cessation, inhibition of platelet aggregation declines to <10% within 4.5 days.1277

**Recommendations**

According to pharmacological characteristics, we suggest that the management of ticagrelor may be comparable to clopidogrel (i.e. withdrawal interval of 5 days). 2C

Platelet transfusion may be ineffective for treating bleeding clearly related to ticagrelor when given 12 h before. 2C

The PLATO trial conducted in 18 000 ACS patients showed reduced mortality from vascular causes, myocardial infarction and stroke with ticagrelor compared with clopidogrel.887 Ticagrelor increased the rate of bleeding unrelated to surgical procedures but did not increase the overall rate of major bleeding.

No studies on efficacy of platelet transfusion in patients treated with ticagrelor were retrieved. When ticagrelor has been administered within the preceding 12 h, its presence in plasma may render platelet transfusion ineffective.

9.3 Anticoagulant agents

9.3.1 Heparin

Heparin is used in clinical practice as unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) and it is necessary to distinguish between the two when making recommendations.
9.3.1.1 Unfractionated heparin
UFH is a heterogeneous mixture of branched glycosaminoglycans; its mean molecular weight is approximately 15 000 Da (range 3000–30 000 Da). UFH binds antithrombin and thrombin, forming a complex which inactivates thrombin and coagulation factors Xa, IXa, Xla and XIIa.

UFH may be administered intravenously or subcutaneously. With intravenous administration, the half-life is >1 h (70–100 min). With subcutaneous administration, the onset of anticoagulation is delayed by approximately 1 h and peak plasma concentrations are reached at 3 h. Clearance occurs via binding to endothelial cells and macrophages, followed by renal metabolism. The process is non-linear and dose-dependent with a half-life after the intravenous administration of a therapeutic dose ranging from 70–100 min.

Indications for UFH include perioperative thromboprophylaxis (US more than Europe), deep vein thrombosis (DVT) or pulmonary embolism, anticoagulation in CPB (extracorporeal pump) or haemodialysis, coronary pathology (unstable angina, myocardial infarction) and disseminated intravascular coagulation.

Recommendations
We recommend that severe bleeding associated with intravenous UFH should be treated with intravenous protamine at a dose of 1 mg per 100 IU UFH given in the preceding 2–3 h. IA

We suggest that severe bleeding associated with subcutaneous UFH unresponsive to intravenous protamine at a dose of 1 mg per 100 IU UFH could be treated by continuous administration of intravenous protamine, with dose guided by aPTT. 2C

Rapid, effective reversal of UFH can be achieved using intravenous protamine (1 mg protamine neutralises 100 IU of UFH). When UFH has been infused continuously, the dose of protamine should be calculated from the UFH dose administered during the preceding 2–3 h. Protamine can cause hypotension and bradycardia, but slow administration (over 1–3 min) reduces the risks. Protamine is less effective with subcutaneously administered UFH, necessitating continuous and prolonged infusion of protamine.

Activated partial thromboplastin time (aPTT) and/or the plasma concentration of anti-FXa are typically used to monitor the effect of usual therapeutic doses of UFH, for higher doses (e.g. in cardiac surgery), activated clotting time is the preferred measurement.

9.3.1.2 Low molecular weight heparins
LMWHs are obtained from UFH by chemical or enzymatic depolymerisation. They are widely employed in clinical practice due to their favourable risk/benefit profile, once-daily dosing and reduced requirement for monitoring.

LMWHs include bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, reviparin and tinzaparin. These products differ in molecular weight, pharmacokinetics, anti-FIIa/anti-FXa activity and approved indications, but recommendations apply equally to all LMWHs.

LMWHs bind to and activate antithrombin. Unlike UFH, not all LMWH molecules can inhibit thrombin (only those with ≥18 saccharides). The anticoagulant action of LMWH is therefore based mainly on FX inhibition. Unlike UFH, LMWHs have low platelet interaction.

LMWHs have almost 100% bioavailability after subcutaneous administration. Peak plasma concentration is reached approximately 3–4 h after administration and the elimination half-life is around 4–6 h (assuming normal renal function).

Monitoring the anticoagulant effects of LMWH is usually unnecessary and can be achieved by measuring plasma anti-FXa activity (only necessary in some special cases such as severe renal insufficiency, morbid obese patients or pregnancy).

Recommendations
We suggest that severe bleeding related to subcutaneous LMWH should be treated with intravenous protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered. 2C

We suggest that severe bleeding associated with subcutaneous LMWH and unresponsive to initial administration of protamine could be treated with a second dose of protamine (0.5 mg per 100 anti-FXa units of LMWH administered). 2C

Protamine administration does not completely reverse LMWH anticoagulation; although it neutralises anti-FIIa activity, it has limited effects on anti-FXa activity. This is because protamine binds poorly to small LMWH fragments with 8–14 saccharides. The clinical significance of this is unclear and there are few data describing protamine in LMWH-related human haemorrhage. In clinical practice, protamine (1 mg per 100 anti-FXa units of LMWH administered; conversion of enoxaparin: 40 mg = 4000 international anti-FXa units) is suggested if haemorrhage occurs within 8 h of LMWH administration. A second dose of protamine (0.5 mg per 100 anti-FXa units administered) may be administered if bleeding continues.

9.3.2 Fondaparinux
Fondaparinux is a synthetic analogue of the pentasaccharide sequence found in UFH or LMWH, with selective action against FXa. It binds to antithrombin and enhances antithrombin inhibition of FXa. Thrombocytopenia is unlikely to occur in patients receiving fondaparinux.
Fondaparinux is indicated for preventing venous thromboembolism (VTE), for initial treatment of VTE and for myocardial infarction.

The anti-FXa activity of fondaparinux is higher than that of LMWH. Administered subcutaneously, fondaparinux has an elimination half-life of 17 h in patients without renal impairment (21 h in elderly patients), allowing once-daily administration. Peak plasma concentration occurs 1.7 h after subcutaneous administration.

Routine coagulation monitoring is not recommended but, as with LMWH, it may occasionally be useful to determine anti-FXa activity (e.g. patients with renal insufficiency).

**Recommendation**

We suggest that the administration of rFVIIa could be considered to treat severe bleeding associated with subcutaneous administration of fondaparinux (off-label treatment). 2C

No drug acts as an antidote to fondaparinux. rFVIIa has been proposed to control severe bleeding, but no evidence exists to support this. 2C

### 9.3.3 Vitamin K antagonists (VKAs)

VKAs are used in patients with mechanical heart valves, atrial fibrillation or venous thromboembolic disease. Long-acting VKAs are used more commonly than acenocoumarol (Table 2).

**Recommendations**

We recommend that vitamin K antagonists (VKAs) should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery (mainly anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in VKA-treated patients. 1C

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score <2 and patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring INR <1.5, VKA should be stopped 5 days before surgery. No bridging is needed. Measure INR on the day before surgery and give 5 mg oral vitamin K if INR exceeds 1.5. 1C

We recommend bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score >2, patients with recurrent VTE treated for <3 months, patients with a mechanical valve). Day 5: last VKA dose; Day 4: no heparin; Days 3 and 2: therapeutic subcutaneous LMWH twice daily or subcutaneous UFH twice or thrice daily; Day 1: hospitalisation and INR measurement; Day 0: surgery. 1C

We recommend that for groups 1 and 2 above, VKAs should be restarted during the evening after the procedure. Subcutaneous LMWH should be given postoperatively until the target INR is observed in two measurements. 1C

We recommend that for group 3 above, heparin (UFH or LMWH) should be resumed 6–48 h after the procedure. VKA can restart when surgical haemostasis is achieved. 1C

We recommend that in VKA-treated patients undergoing an emergency procedure or developing a bleeding complication, PCC (25 IU FIX kg⁻¹) should be given. 1B

VKA treatment is monitored by measuring INR. Before surgical intervention, INR should be brought below 1.5. VKA treatment may be interrupted before elective surgery and resumed after surgery (with the first meal). Postoperative heparin is given if the INR is <2. For urgent surgery, PCC (25 IU FIX kg⁻¹) should be given, and additional administration of 5 mg vitamin K1 (intravenous, subcutaneous or oral) is recommended.

### 9.3.4 Oral inhibitor of activated thrombin

Dabigatran etexilate (Pradaax, Boehringer Ingelheim, Ingelheim am Rhein, Germany) is the only available oral antithrombin drug, and is licensed throughout Europe for use in orthopaedic surgery. The bioavailability of dabigatran etexilate is 6–8%, its T_{max} is 2 h and its terminal half-life is 14–17 h. Dabigatran is renally eliminated and exhibits no interaction with food. 1C

Two pivotal orthopaedic surgical studies have shown the efficacy of once-daily oral dabigatran (150 mg or 220 mg) to be as effective as subcutaneous enoxaparin. Both drugs had similar safety profiles, with no signs of hepatotoxicity. A third study, comparing identical doses of dabigatran and enoxaparin (30 mg twice daily), failed to demonstrate equivalence, because more distal thromboses were observed with dabigatran. However, rates of proximal thrombosis, major bleeding and symptomatic events did not differ between dabigatran and enoxaparin.

The efficacy of dabigatran has been demonstrated in atrial fibrillation patients; in a large study with a 2-year follow-up, the frequency of primary outcomes (stroke or systemic embolism) was 1.53% per year with 110 mg dabigatran twice-daily and 1.11% per year with 150 mg
Relative risk with 110/150 mg dabigatran was investigated dabigatran neutralisation using a
elimination of apixaban is

An increased

Safety will remain a concern until high quality data are available. A specific anti-FXa activity test will become
available for monitoring rivaroxaban therapy.

No antidote to rivaroxaban is available. Proposed therapy for major bleeding includes PCC and rFVIIa. No patient
data exists which support this proposal, although PCC effectiveness has been demonstrated in healthy
volunteers. FXa analogues, which could potentially reverse
anti-FXa agents, are currently being developed. In
emergencies, it may be necessary to wait for two half-lives (14–26 h) to allow rivaroxaban to fall to acceptable
concentrations. However, this is merely a fallback solution.

9.3.5 Oral direct factor Xa inhibitors
Several activated factor X (FXa) inhibitors are now marketed or in advanced stages of development.

9.3.5.1 Rivaroxaban
Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin-Wedding, Germany) is an orally active oxazolidone
derivative and the first available oral anti-FXa agent. It is a potent anticoagulant with a wide therapeutic window. Rivaroxaban has a bioavailability of 80% and a $T_{\max}$ of 2–4 h. Rivaroxaban inhibits FXa ($K_i$ 0.4 nM) and binds to both free and clot-bound FXa. Two-thirds of rivaroxaban is renally eliminated; its half-life is 9–13 h.

The incidence of thromboembolic events was 49% lower (9.6% vs. 18.9%) in knee arthroplasty patients who received rivaroxaban (10 mg once-daily) compared with 40 mg enoxaparin (RECORD3 study). An increased bleeding incidence was not observed with rivaroxaban. In the RECORD1 study (35 days of prophylaxis after hip surgery), the primary efficacy outcome occurred in 1.1% of patients who received rivaroxaban compared with 3.7% in the enoxaparin group ($P < 0.001$). Major VTE occurred in 0.2% of patients receiving rivaroxaban and 2.0% of patients receiving enoxaparin ($P < 0.001$). Major bleeding affected 0.3% of patients receiving rivaroxaban compared with 0.1% receiving enoxaparin ($P = 0.18$), although bleeding at the surgical site was not classified as major bleeding. By integrating the surgical site, it was found that haemorrhage occurred more frequently with rivaroxaban than with enoxaparin.

A study of high-risk patients with atrial fibrillation (ROCKET-AF trial) used a composite endpoint of all-cause stroke and non-central nervous system systemic embolism. Rivaroxaban 20 mg once-daily, showed comparable benefits to warfarin (2.12% vs. 2.42%; $P < 0.001$ for non-inferiority). Rates of major bleeding were comparable between rivaroxaban and warfarin (3.60% vs. 3.45%; $P = 0.576$). Compared with warfarin, patients receiving rivaroxaban suffered fewer intracranial haemorrhages (0.49% vs. 0.74%; $P = 0.019$), fewer critical organ bleeds (0.82% vs. 1.18%; $P = 0.007$) and fewer bleeding-related deaths (0.24% vs. 0.48%; $P = 0.003$).

Oral rivaroxaban alone (15 mg twice-daily for 3 weeks, then 20 mg once-daily) has been compared with subcutaneous enoxaparin followed by oral VKA (warfarin or acenocoumarol) for 3, 6 or 12 months for the treatment of DVT (EINSTEIN DVT study). Rivaroxaban displayed non-inferiority in the primary efficacy outcome (56 events [2.1%] vs. 51 events [3.0%] with enoxaparin/VKA; $P < 0.001$). The principal safety outcome occurred in 8.1% of patients in each group.

The lack of biological monitoring with dabigatran could be considered as progress but may also bring insecurity to physicians. A thrombin inhibitor assay (Hemoclot; Aniara, West Chester, OH) is now available to monitor dabigatran therapy.

No antidote is available for dabigatran etexilate. Dialysis has been shown to be effective to remove dabigatran. Treatments proposed for bleeding include PCC and rFVIIa, but neither has been tested clinically. Van Ryn et al. investigated dabigatran neutralisation using a selective antibody; clinical data are awaited. In emergencies, it may be advisable to wait for two half-lives (34 h) for dabigatran concentrations to reach acceptable concentrations. However, given widely varying interindividual elimination rates, this is merely a fallback solution.
The primary efficacy outcome occurred in 15.1% of patients receiving apixaban and 24.4% receiving enoxaparin \( (P < 0.001) \). Major VTE occurred in 1.1% of patients treated with apixaban and 2.2% of patients treated with enoxaparin \( (P = 0.019) \). Clinically relevant bleeding occurred in 3.5% of patients receiving apixaban and 4.8% of patients given enoxaparin \( (P = 0.09) \). In hip replacement patients (ADVANCE-3 study), the relative risk reduction with apixaban was 64% \( (1.4\% \text{ vs. } 3.9\%, \quad P < 0.0001) \). Apixaban was also statistically superior to a 40 mg dose of enoxaparin for preventing major VTE \( (0.45\% \text{ vs. } 1.14\%; \quad P = 0.0054) \). Bleeding event rates were similar for both treatment groups.

A large development programme for apixaban is now almost completed. In patients with atrial fibrillation, the AVERROES study\(^{492} \) was stopped prematurely because apixaban reduced the risk of stroke or systemic embolism by 57% compared with aspirin, with no significant increase in major haemorrhage risk. The ARISTOTLE study\(^{1300} \) compared apixaban and warfarin in 18 201 patients with atrial fibrillation. The rate of the primary outcome (ischaemic or haemorrhagic stroke, or systemic embolism) was 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% CI, 0.66–0.95; \( P = 0.01 \) for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60–0.80; \( P < 0.001 \)), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80–0.99; \( P = 0.047 \)).

For biological monitoring, assessment of anti-FXa may be useful (Table 3).

No antidote to apixaban is available. FXa analogues, which could potentially reverse the effects of anti Xa agents, are being developed. In emergencies, it may be necessary to wait for two half-lives \( (10–22 \text{ h}) \) to allow edoxaban to reach acceptable concentrations. However, given wide variability in interindividual elimination rates, this is merely a fallback solution.

### 9.3.6 Management of patients scheduled for a procedure and treated with new oral anticoagulant agents (emergency procedures excluded)

Physicians from outside the field may be unaware of the pharmacological characteristics of many new oral anticoagulant agents (NOAs). A multidisciplinary, international group of physicians (Groupe d’Intérêt en Hémostase Périopératoire) has issued proposals for managing patients treated with NOAs.\(^{1078} \) As for VKA therapy, three patient groups are considered.

**Recommendations**

We recommend to assess creatinine clearance in patients receiving NOAs and being scheduled for surgery. \( 1B \)

We suggest that NOAs should not be interrupted for skin surgery, dental and other oral procedures, gastric and colonic endoscopies (even if biopsy is scheduled, but not polypectomy), nor for most ophthalmic surgery, (mainly

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**Table 3 Comparison of new oral antithrombotic agents**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Daribagran Eletexeite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td><strong>Brand name</strong></td>
<td>Xarelto</td>
<td>Eliquis</td>
<td>Liviana</td>
<td>Pradaxa</td>
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<td><strong>Route of administration</strong></td>
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<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
<td>51–85%</td>
<td>60%</td>
<td>6–8%</td>
</tr>
<tr>
<td><strong>T\text{max}</strong></td>
<td>2–4 h</td>
<td>3 h</td>
<td>1–3 h</td>
<td>2 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>9–13 h</td>
<td>9–14 h</td>
<td>5–11 h</td>
<td>14–17 h</td>
</tr>
<tr>
<td><strong>Frequency of administration</strong></td>
<td>Once-daily</td>
<td>Twice-daily</td>
<td>Once-daily</td>
<td>Once- or twice-daily</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>66% (half inactive)</td>
<td>25%</td>
<td>36–45%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
anterior chamber, e.g. cataract), although vitreoretinal surgery is sometimes performed in NOA-treated patients. 2C

We recommend that for low-risk patients (e.g. atrial fibrillation patients with CHADS2 score <2, patients treated for >3 months for a non-recurrent VTE) undergoing procedures requiring normal coagulation (normal diluted thrombin time or normal specific anti-FXa level), NOAs can be stopped 5 days before surgery. No bridging therapy is needed. 1C

In patients treated with rivaroxaban, apixaban, edoxaban and in patients treated with dabigatran in which creatinine clearance is higher than 50 ml min⁻¹, we suggest bridging therapy for high-risk patients (e.g. atrial fibrillation patients with a CHADS2 score >2, patients with recurrent VTE treated for <3 months). Day –5: last NOA dose; Day –4: no heparin; Day –3: therapeutic dose of LMWH or UFH; Day –2: subcutaneous LMWH or UFH; Day –1: last injection of subcutaneous LMWH (in the morning, i.e. 24 h before the procedure) or subcutaneous UFH twice daily (i.e. last dose 12 h before the procedure), hospitalisation and measurement of diluted thrombin time or specific anti-FXa; Day 0: surgery. 2C

In patients treated with dabigatran with a creatinine clearance between 30 and 50 ml min⁻¹, we suggest to stop NOAs 5 days before surgery with no bridging therapy. 2C

We suggest that for groups 2 and 3, heparin (UFH or LMWH) should be restarted 6–72 h after the procedure, taking the bleeding risk into account. NOAs may be resumed when surgical bleeding risk is under control. 2C

10 PERIOPERATIVE BLEEDING MANAGEMENT IN PATIENTS WITH COMORBIDITIES WITH HAEMOSTATIC DERANGEMENTS AND CONGENITAL BLEEDING DISORDERS

10.1 Patients with comorbidities involving haemostatic derangement

10.1.1 Systemic, metabolic and endocrine diseases

Recommendation

We suggest that patients with haemostatic derangements associated with systemic, metabolic and endocrine diseases should be managed perioperatively in collaboration with a haematologist. 2C

Systemic, metabolic and endocrine diseases (e.g. amyloidosis, hypothyroidism) are associated with haemostatic derangements. Optimal management strategies for these coagulopathies remain unclear.

Acquired FX deficiency causes the most frequent bleeding manifestations in amyloidosis and is treated similarly to inherited FX deficiency.

Bleeding diathesis in overt hypothyroidism is mainly due to acquired type 1 VWD. In a study of patients with thyroid disease, all responded favourably to desmopressin. 1305

10.1.2 Patients on chronic medication associated with haemostatic derangements

Medications other than antiplatelet and anticoagulant agents (discussed elsewhere in these guidelines – see section 9) may potentially affect haemostasis, including selective serotonin reuptake inhibitors (SSRIs), valproic acid and Ginkgo biloba.

Recommendation

We suggest that SSRI treatment should not be routinely discontinued perioperatively. 2B

SSRIs have been associated with an increased bleeding tendency, due to serotonin depletion from platelets. 1306 Bleeding frequency appears proportionate to the degree of serotonin reuptake inhibition.

In patients undergoing orthopaedic surgery, intraoperative blood loss increased by 75% among patients using SSRIs, and the risk of blood transfusion almost quadrupled (adjusted odds ratio, 3.71). Patients taking non-serotonergic antidepressants had no increased risk (odds ratio, 0.74). 1307 However, comediations (NSAIDs, methotrexate or iron supplements) also increased transfusion risk.

A study of patients undergoing elective primary total hip arthroplasty reported increased (95 ml or 17%) intraoperative blood loss among SSRi users compared with users of non-serotonergic antidepressants. 1308 However, transfusion requirements were not increased. Similarly, preoperative SSRI therapy has been shown not to increase allogeneic RBC transfusion during CAGB surgery. Adjusted relative risks for transfusion among users of SSRIs, non-selective serotonin reuptake inhibitor antidepressants and other antidepressants were 1.1, 0.9, and 1.0, respectively, compared with patients not using antidepressants. 1309 A retrospective Australian study performed on 4136 patients who underwent CAGB surgery also showed that neither SSRI use, nor SSRi and concomitant antiplatelet medication, increased the risk of any bleeding events. 1310 However, in a large cohort study, it has been shown that patients taking an SSRI together with aspirin or dual antiplatelet therapy following acute myocardial infarction were at increased risk of bleeding. 1311 Therefore, discontinuation of SSRIs before surgery is not recommended. 1312 When used alongside other antiplatelet agents, perioperative use of SSRIs should be individualised.

Recommendation

We suggest individualised perioperative discontinuation of antiepileptic agents, such as valproic acid, which may increase bleeding. 2C

The antiepileptic drug valproic acid decreases levels of FVII, FVIII, FXIII, platelets, VWF, fibrinogen, protein C
and antithrombin. However, clinically relevant detriment to haemostasis is uncommon.

**Recommendation**

*We do not recommend discontinuation of Gingko biloba extracts.*

The effects on blood coagulation have been questioned due to some case reports of spontaneous bleeding after taking Ginkgo preparations. A meta-analysis of 18 randomised controlled trials did not indicate a higher bleeding risk associated with standardised Gingko biloba extracts provided as daily oral therapy.

Ginkgo biloba combined with aspirin also has no impact on coagulation indices.

**10.2 Patients with congenital bleeding disorders**

**10.2.1 Von Willebrand disease**

VWD is the most common hereditary bleeding disorder with an estimated prevalence of 0.6–1.3%. The disease is caused by deficiency or dysfunction of VWF and is classified into three major categories, which are specifically treated: partial quantitative deficiency (type 1); qualitative deficiency (type 2, with four variants: 2A; 2B; 2M; and 2N); and total deficiency (type 3).

Acquired von Willebrand syndrome comprises defects in VWF concentration, structure or function arising from medical disorders or treatments. Bleeding in VWD is due to impaired platelet adhesion and/or reduced levels of FVIII and is usually mild.

**10.2.1.1 Preoperative evaluation**

**Recommendations**

*We suggest that if VWD is suspected preoperatively, the patient should be referred to a haematologist for assessment and planning of the intervention.*

*We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding.*

Diagnosis of VWD is complex, and no universal approach applies. Initial tests for diagnosing VWD include VWF ristocetin cofactor activity (VWF:RCo), VWF antigen (VWF:Ag) and FVIII coagulant activity (FVIII:C). Laboratory testing should be guided by history and physical examination.

Structured questionnaires and bleeding scores are useful for the diagnosis. A quantitative bleeding assessment tool (BAT) has been evaluated for diagnosing mild bleeding disorders (MBDs). The positive predictive values in patients referred for haemostatic or familial evaluation were 71.0% and 77.5%, respectively. Bleeding scores ≤5 had a high negative predictive value which increased to 99.6% when aPTT measurement was added. Therefore, exclusion of MBDs may be feasible based on BAT and aPTT. In children, the bleeding scores have also limited predictive value for identifying patients with common MBDs but high negative predictive values.

However, questionnaires can be used to assess bleeding severity of VWD. A mucocutaneous bleeding score (spontaneous, mucocutaneous symptoms) was at least as effective as laboratory testing (circulating levels of VWF and FVIII:C) for predicting bleeding after tooth extraction, and superior to laboratory testing following surgery. In children with VWD, the median bleeding score has been reported as 7, compared with 0 in controls. The most frequent clinically significant bleeding symptoms were surgical bleeding, bleeding after tooth extraction and menorrhagia.

**10.2.1.2 Perioperative management**

**Recommendations**

*We recommend that patients with VWD be managed perioperatively in collaboration with a haematologist.*

Reviews and guidelines covering the management of VWD have been published. All agree that patients should be managed in specialised centres. However, recommendations for the diagnosis and treatment of VWD are based on observational studies and case series, and are therefore of low grade.

There are three strategies to prevent or control bleeding in VWD: release stored endogenous VWF by stimulating endothelial cells with desmopressin; replace VWF using plasma-derived concentrates; or promote haemostasis with antifibrinolytic drugs or platelet transfusion.

The National Heart, Lung, and Blood Institute guidelines recommend the following:

1. Treat minor bleedings with desmopressin after a trial performed before clinical use.
2. Use VWF concentrate if the response to desmopressin is inadequate.
3. Administer desmopressin and VWF concentrate based on VWF:RCo and FVIII activity concentrations.
4. For severe bleeding or prophylaxis for major surgery, VWF:RCo and FVIII levels should be 100–200 IU dl⁻¹ and 100–250 IU dl⁻¹, respectively. Subsequent dosing should maintain VWF:RCo and FVIII levels above 50 IU dl⁻¹ for 7–10 days.
5. For prophylaxis for minor surgery, VWF:RCo and FVIII levels should be >50 IU dl⁻¹ (preferably >50 IU dl⁻¹) with maintenance for 1–5 days.
6. For oral surgery in mild–moderate VWD, combined desmopressin and antifibrinolytic drugs should be given.
7. Restrict fluids to maintenance levels in young children and surgical patients receiving desmopressin.

Italian guidelines are similar, except for the lower target and peak concentrations of FVIII recommended for
prophylaxis before major surgery and to be avoided for preventing the risk of thrombosis, respectively.\textsuperscript{1330} Other European centres recommend that guidelines should be stratified for the severity of bleeding, the type of surgery and also for the bleeding score in either VWD type 1, 2 or 3.\textsuperscript{1332}

**Recommendation**

*We recommend desmopressin as a first-line treatment for minor bleeding/surgery in patients with VWD, after a trial testing. Treatment regimens are specified by published guidelines. 1C*

Despite a lack of RCTs investigating desmopressin in VWD, desmopressin has been shown to increase plasma VWF and FVIII concentrations from two-fold to more than five-fold over baseline concentrations, with good and excellent results in most surgical adult patients\textsuperscript{1333–1336} as well as children.\textsuperscript{1337–1339}

The standard desmopressin dose is 0.3 \(\mu\)g kg\(^{-1}\) given intravenously, repeated every 12–24 h.\textsuperscript{1320} Response rates are reduced in children <2 years old.\textsuperscript{1337}

Desmopressin is usually effective in type 1 VWD; however, not all patients respond to this agent.\textsuperscript{1320} In a type 1 VWD cohort (\(n = 77\)), 83\% of patients displayed a complete response to desmopressin; 13\% exhibited a partial response and 4\% had no response.\textsuperscript{1333} Similarly, a 17\% risk of bleeding complications after adenosintosillar procedures was reported in children receiving prophylactic desmopressin.\textsuperscript{1340} These studies reinforce the importance of a preoperative test infusion of desmopressin.

Desmopressin is variably effective in types 2A, 2N and 2M VWD, ineffective in type 3 VWD\textsuperscript{1330} and controversial in type 2B VWD.\textsuperscript{1321}

Tachyphylaxis and hyponatraemia are frequent adverse effects of desmopressin.\textsuperscript{1321,1332} Arterial thrombosis has also been reported anecdotally.\textsuperscript{1341} Hyponatraemia and seizures have been reported in paediatric cases.\textsuperscript{1338}

**Recommendation**

*We recommend replacement of VWF with plasma-derived products for major bleeding/surgery. Treatment regimens are specified by published guidelines. 1C*

VWF can be supplied by cryoprecipitate or human plasma-derived concentrates. Cryoprecipitate is not virus-inactivated and its use is strongly discouraged, except in life-threatening situations when concentrates are not available.\textsuperscript{1320}

Plasma-derived VWF concentrates may prevent excessive bleeding in over 90\% of VWD patients.\textsuperscript{1321} The efficacy has been confirmed in surgical paediatric\textsuperscript{1342,1343} and adult patients with VWD.\textsuperscript{1336,1343–1350}

For bleeding treatment/prevention in major surgery, a loading dose of 40–60 U kg\(^{-1}\) is recommended, with 20–40 U kg\(^{-1}\) every 8–24 h for maintenance.\textsuperscript{1320} For minor surgery, the doses are slightly lower, given less frequently and for a shorter duration. Treatment of VWD-related bleeding with VWF concentrates should take account of individual product content and pharmacokinetic data for the relevant disease severity.\textsuperscript{1351}

Perioperative monitoring of FVIII:C and VWF:RCO may help determine appropriate dosing.\textsuperscript{1320} Depending on VWD type and the concentrate used, PFA-100 might be useful for monitoring the response to FVIII/VWF substitution.\textsuperscript{1352}

Adverse reactions to VWF concentrates include allergic and anaphylactic reactions.\textsuperscript{1343}

VWF concentrates contain FVIII, and therefore carry a potential thromboembolic risk.\textsuperscript{1353} Antithrombotic prophylaxis should be considered.\textsuperscript{1341}

**Recommendation**

*We suggest that antifibrinolytic drugs should be used as haemostatic adjuncts. Treatment regimens are specified by published guidelines. 2C*

Antifibrinolytic therapy may facilitate effective clotting. Evidence supporting local application of antifibrinolytics is limited, but this treatment has a pharmacodynamic rationale.\textsuperscript{1354} Adjuvant local therapy with tranexamic acid added to desmopressin prevented bleeding complications during oral surgery in 84\% of VWD patients and reduced the need for factor concentrates.\textsuperscript{1334}

For adults, a dose of 4–5 g EACA (oral or intravenous) is recommended, followed by 1 g h\(^{-1}\) until bleeding is controlled, or for 5–7 days postoperatively.\textsuperscript{1321} Tranexamic acid is given intravenously at a dose of at 10 mg kg\(^{-1}\) every 8–12 h.\textsuperscript{1320,1321,1330}

**Recommendation**

*We suggest that platelet transfusion should be used only in case of failure of other treatments. 2C*

When haemorrhage persists despite increased VWF/FVIII levels, administration of platelet concentrate can be helpful.\textsuperscript{1355} Platelet concentrates are effective, particularly in patients with type 3 VWD, probably because of their role in transporting VWF to sites of vascular injury.\textsuperscript{1321}

### 10.2.2 Platelet defects

Many classification schemes have been proposed for inherited platelet disorders.\textsuperscript{1336,1337} They are uncommon conditions which can alter circulating platelet numbers, function or both. Prominent inherited platelet defects include Glanzmann thrombasthenia (deficiency or functional defect of receptor GPIIb/IIIa) and Bernard-Soulier syndrome (dysfunction or absence of receptor GPIb/IX/V). Both conditions may cause severe bleeding.\textsuperscript{1336,1338,1339}

Bleeding with other platelet abnormalities is usually mild/moderate, so they are described as MBDs;\textsuperscript{1359}
VWD is included in this category. Typically, they manifest as mucocutaneous bleeding, or bleeding following trauma or invasive surgical or dental procedures.

10.2.2.1 Preoperative evaluation

Recommendations

We suggest referring the patient to a haematologist for assessment and planning of the intervention if inherited platelet defects are suspected preoperatively. 2C

We recommend the use of bleeding assessment tools for predicting the perioperative risk of bleeding. 1C

Diagnosis of platelet defects is challenging. Bleeding history is a prerequisite for diagnosing bleeding disorders and should inform the selection of laboratory investigations. However, MBDs may be undetectable from the bleeding history. Bleeding scores and quantitative BATs have been proposed for diagnosing MBDs. Prospective studies found that structured bleeding questionnaires have a high negative predictive value but a low/moderate positive predictive value both in adults and in children referred for diagnosis. Measurement of aPTT in addition to a bleeding score significantly increased the diagnostic efficiency for exclusion of patients with suspected MBD in a low-prevalence setting.

In children, it was shown that questionnaire scores differ among diagnostic groups, giving the potential for stratification of bleeding severity and therefore prediction of bleeding risk during surgical or dental procedures. However, no relationship is apparent between bleeding severity and VWF/platelet function variables and the diagnostic efficacy of laboratory testing for hereditary mucocutaneous bleeding was 40.4%. Therefore, platelet function defects constitute risk factors rather than the unequivocal causes of haemorrhage.

PFA-100 has a high rate of false positive and false negative results and does not predict bleeding risk. The C-EPI parameter is not sufficiently sensitive to be recommended as a haemostasis screening test, although it correlates with severity of bleeding history.

Furthermore, no consensus currently exists regarding the standardisation and interpretation of in vitro platelet aggregation/secretion studies for the definitive diagnosis of a platelet defect.

10.2.2.2 Perioperative management

Recommendations

We recommend that patients with severe inherited platelet disorders should be managed perioperatively in collaboration with a haematologist. 1C

We suggest preoperative haemostatic correction in patients with inherited platelet disorders. 2C

Most MBDs respond to desmopressin and/or antifibrinolytic drugs, regardless of aetiology. However, platelet function disorders require specialist management.

The benefits of prophylactic correction of congenital platelet dysfunction were shown in a prospective study including 72 patients with impaired primary haemostasis. Patients with inherited primary haemostatic impairment (platelet dysfunction including VWD) were preoperatively treated with desmopressin. Most non-responders, defined by persistently abnormal PFA-100 platelet function tests, additionally received tranexamic acid or aprotinin; those with VWD were treated with VWF concentrate, conjugated oestrogens and platelet transfusion. In almost all cases, prophylactic treatment successfully corrected PFA-100 parameters. The frequency of blood transfusion was lower (9.4% vs. 12.2%; P = 0.202) in preoperatively treated patients with impaired haemostasis than in patients without impaired haemostasis. In a retrospective group, the frequency of blood transfusion was significantly higher (89.3% vs. 11.3%; P < 0.001) in patients without preoperative correction of impaired haemostasis than in patients without impaired haemostasis. Thus, preoperative correction of impaired primary haemostasis appears possible in most patients, and reduces homologous blood transfusions.

Recommendation

We suggest that desmopressin should be used to prevent/control perioperative bleeding in patients with inherited platelet defects. 2C

The more common, less severe platelet disorders typically respond well to desmopressin, either prophylactically before elective procedures or following trauma. Desmopressin shortens bleeding time and is therefore assumed to provide clinical benefit.

Most evidence supporting the clinical efficacy of desmopressin in platelet disorders comes from case reports or small case series, and only one old placebo-controlled study. The latter study found that desmopressin shortened bleeding time and was sufficient for perioperative management, dependent on the underlying platelet defect. Desmopressin has also been reported as haemostatically effective during obstetric delivery in patients with mild platelet defects. However, efficacy appears variable, both in mild and in severe platelet defects, and has rarely been shown in Glanzmann thrombasthenia.

If desmopressin is contraindicated or is not effective, patients should receive platelet transfusion or possibly rFVIIa.

Recommendation

We suggest that antifibrinolytic drugs should be used as haemostatic adjuncts in procedures involving patients with inherited platelet defects. 2C
Antifibrinolytic drugs are useful as adjunctive therapy;\textsuperscript{1356,1357} minor bleeding (e.g., dental procedures) may respond to these agents alone.\textsuperscript{1358} The use of antifibrinolytic drugs in inherited platelet disorders is not evidence-based. However, tranexamic acid can partially reverse effects of clopidogrel in cardiac surgery.\textsuperscript{12}

\textbf{Recommendation}

\textit{We recommend that rFVIIa treatment should be considered in patients with Glanzmann thrombasthenia undergoing surgery. 1C}

rFVIIa is licensed for use in Glanzmann thrombasthenia, in which platelet transfusion may be ineffective. Appropriate dosing may be 90 $\mu$g kg\textsuperscript{-1} immediately preoperatively, repeated every 2 h for 12 h, then every 3–4 h until the risk of rebleeding subsides.\textsuperscript{1356} An international registry including 59 patients with Glanzmann thrombasthenia showed that rFVIIa was effective in 29/31 surgical procedures and in 77/103 bleeding episodes, eight of which recurred.\textsuperscript{1358} Increased success was observed in severe bleeding episodes when a regimen including $\geq 80 \mu$g kg\textsuperscript{-1} by injection, a dosing interval $\leq 2.5$ h and $\geq 3$ doses before failure declaration, was used. Patients receiving maintenance doses experienced fewer bleeding recurrences within 48 h than those not receiving maintenance doses. One thromboembolic event and one ureteral blood clot occurred with high-dose rFVIIa. Further thrombotic complications related to rFVIIa therapy have been reported.\textsuperscript{1031}

No reliable data exist concerning rFVIIa in bleeding due to platelet dysfunction and the drug is not licensed for other platelet disorders. In one study, rFVIIa was used in children with inherited platelet function disorders: Glanzmann thrombasthenia ($n = 5$); Bernard–Soulier syndrome ($n = 1$); and storage pool disease with severe phenotype ($n = 1$).\textsuperscript{1369} Variable results were seen in Glanzmann thrombasthenia, although surgical procedures were successfully covered. Importantly, good/excellent responses were observed in 10/14 bleeding episodes (71%) treated within 12 h, but only 2/11 (18%) treated after 12 h.

In another study, patients with Glanzmann thrombasthenia with bleeding episodes or undergoing dental surgery were treated with antifibrinolytic drugs, with or without additional rFVIIa. In most cases of mild/moderate mucocutaneous bleeding, antifibrinolytic drugs and local measures were considered sufficiently effective, rendering rFVIIa unnecessary.\textsuperscript{1370} However, prophylactic administration of rFVIIa was effective in avoiding bleeding during teeth extractions.

\textbf{Recommendations}

\textit{We recommend against routine platelet transfusion in patients with inherited platelet disorders. 1C}

\textit{There is insufficient evidence to recommend a threshold for perioperative prophylactic platelet transfusion in thrombocytopaenic patients. C}

Platelet transfusions are appropriate in severe platelet defects and when other options have failed. Due to uncertainty concerning rFVIIa efficacy, platelets are recommended for major elective surgery in patients with Glanzmann thrombasthenia and Bernard–Soulier syndrome.\textsuperscript{1356,1364} First doses should be given preoperatively with further doses depending on clinical need. For emergency procedures, random donor platelets may be given, albeit with a high risk of alloimmunisation which can limit future responses.\textsuperscript{1365}

Inherited thrombocytopaenias are generally managed similarly to mild platelet disorders.\textsuperscript{1371} Thrombocytopaenic patients without evidence of platelet dysfunction should be treated according to platelet count. Platelet transfusion guidelines recommend $\geq 50 \mu$g kg\textsuperscript{-1} for liver biopsy, laparotomy, central line insertion and for major surgery, except ophthalmological and neurological surgery, when $\geq 100 \mu$g kg\textsuperscript{-1} is recommended.\textsuperscript{1372} Transfusions are usually effective if platelet count is raised above 20 000–30 000 $\mu$g l\textsuperscript{-1}.

Although guidelines recommend a preoperative platelet transfusion threshold of $< 50 \mu$g kg\textsuperscript{-1}, supporting evidence is weak.\textsuperscript{1372} An old study of thrombocytopoenic patients with acute leukaemia showed that surgery is safe even in patients with platelet counts $< 50 \mu$g kg\textsuperscript{-1}, provided that optimal supportive care is available.\textsuperscript{1372} Central venous catheters can also be inserted safely in acute leukaemia patients with platelet counts $\geq 20 \mu$g kg\textsuperscript{-1} without platelet transfusion, provided that other coagulation abnormalities are absent.\textsuperscript{1373}

Recent data suggest also administering fewer platelet transfusions, at lower doses. However, a meta-analysis showed that high-dose platelet transfusion ($3.35–7.7 \times 10^{11}$ $\mu$g l\textsuperscript{-1}) increased the transfusion interval compared with low-dose platelet transfusion ($2.01–4.6 \times 10^{11}$ $\mu$g l\textsuperscript{-1}).\textsuperscript{1374} The increase in post-transfusion platelet count was also higher in patients receiving the higher dose, with ABO-compatible transfusions. Although bleeding incidence appeared to be independent of platelet count, the above data coming from haematology-oncology should not be extrapolated to inherited thrombocytopaenia.

\subsection*{10.2.3 Haemophilia A and B}

Haemophilia A is characterised by reduced plasma FVIII coagulant activity (FVIII:C), and Haemophilia B by FIX deficiency. The prevalence of haemophilia A is 1:10 000, compared with 1:60 000 for haemophilia B.\textsuperscript{1375}

Haemophilia patients may develop spontaneous bleeding into joints and bleed excessively after injury or surgery. Clinical severity of the bleeding correlates with the degree of deficiency.\textsuperscript{1376} Haemophilia A is classified as mild, moderate or severe, depending on FVIII:C concentration. Mildly affected patients bleed excessively only after trauma or surgery and may have normal routine coagulation test results.\textsuperscript{1377}
Factor replacement therapy can induce anti-FVIII or anti-FIX antibodies, known as ‘inhibitors’. These are more common in severe forms of haemophilia. Development of inhibitors in mild haemophilia can change bleeding phenotype from mild to severe. Some carrier females have reduced coagulation factor concentrations and this is important when specific replacement therapy may be required.

Acquired haemophilia is a rare but potentially life-threatening haemorrhagic disorder caused by the development of autoantibodies against FVIII. It may be associated with malignancy, autoimmune disorders, drug reactions and pregnancy. Haemophilia therapy involves infusion of coagulation factor concentrates, either prophylactically or during bleeding. Mild haemophilia may be treated with desmopressin and tranexamic acid rather than coagulation factors.

Recommendations

We recommend that haemophilia patients should be referred preoperatively to a haematologist for assessment/intervention. 1C

We recommend that surgery in haemophilia patients should be performed in specialised centres with expertise in coagulation disorders. 1C

With adequate therapy provided in specialised centres, haemophilia patients can safely undergo most surgical procedures. Retrospective cohort studies found the same outcome after orthopaedic surgery or general surgery compared to non-haemophilia controls. General surgical and endoscopic procedures were performed with low morbidity (4% haemarthographic complications) and mortality rates (1.4%) with appropriate factor replacement and good support from the haemophilia team. Surgical procedures are also safe in children with haemophilia provided that a standard protocol is followed.

Recommendations

We recommend adequate perioperative replacement therapy to ensure safe surgery in haemophilia patients. 1C

We suggest that perioperative replacement therapy (target factor levels and duration) in haemophilia patients follows published guidelines. 2C

Few reviews of periprocedural replacement therapy have been published, and consensus recommendations are country-specific. The World Federation of Haemophilia (WFH) recommends that in patients undergoing major surgery, preoperative factor levels should be 80–100%. Postoperatively, factor concentrations should be maintained at 60–80% during days 1 to 3, 40–60% during days 4 to 6 and 30–50% during the second postoperative week. The recommended concentrations for haemophilia B are slightly lower: 60–80%, 40–60%, 30–50% and 20–40%, respectively.

An appropriate factor concentration should be maintained for 5–7 days or until wound healing after minor surgery, and for 10–14 days after major surgery. For minor invasive procedures (lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy), replacement therapy should only be given before the procedure.

A literature review and a survey of European practice were published recently. Although high-quality studies are lacking, replacement therapy appeared efficacious in perioperative management of haemophilia A. The recommendations formulated by the authors are similar to those formulated by the WFH. For liver biopsy, preoperative factor concentrations should be >80% and replacement therapy should continue for ≥3 days. For children undergoing surgery, preoperative factor concentrations should generally be >80% and therapy should be maintained for 7–10 days after tonsillectomy, 3–4 days after circumcision, and ≥3 days after central venous access device insertion. For dental extractions, treatment with clotting factor concentrate is recommended to obtain a minimum factor concentration of 50%.

The European survey also demonstrated extensive heterogeneity in clinical practice. However, in most settings there was agreement between published data and clinical practice concerning the intensity and duration of replacement therapy.

Clinical effects of different coagulation factor concentrations have not been investigated, and minimum haemostatic concentrations of individual factors cannot be defined. Only one study showed that lower factor concentrations may be safe in surgical procedures. Conversely, a high–level clotting factor replacement regimen which maintains the preoperative high concentration for a longer period of time appeared to favour wound healing and to decrease the infection rate in total knee arthroplasty.

FFP and cryoprecipitate have relatively low clotting factor concentrations and potential viral transmission risks. These products are indicated only if concentrates are not available.

Recommendation

We recommend either recombinant products or plasma-derived concentrates for perioperative replacement therapy in haemophilia patients. 1C

Both plasma-derived and recombinant FVIII products proved efficacious for preventing/treating bleeding episodes in haemophilia patients. Although all plasma-derived coagulation factor concentrates have
excellent safety. UK guidelines recommend recombinant, rather than plasma-derived, products.1341

The question of whether plasma-derived or recombinant products are preferable is still under discussion.1390,1391 It has been suggested that plasma-derived products induce fewer inhibitors than recombinant FVIII.1391 One study showed that recombinant FVIII carries a 2.5–3-fold higher risk of inhibitor development than plasma-derived FVIII/VWF.1392 In a paediatric study, increased risk of inhibitor formation was associated with early exposure to recombinant products.1393 Conversely, another study demonstrated no significant difference in risk of inhibitor development between plasma-derived FVIII and recombinant FVIII.1394 In addition, the safety and efficacy of recombinant FVIII has been shown in a post-marketing observational study.1395

Two systematic reviews reported discordant results.1396,1397 A prospective cohort study showed that the degree of FVIII purity but not the source of the product influences inhibitor development independently from other risk factors.1398 In this study there was an increased inhibitor risk with recombinant FVIII and high-purity plasma-derived FVIII compared to low/intermediate-purity plasma-derived FVIII.

In haemophilia B, there is also evidence that both plasma-derived and recombinant products are effective in perioperative management.1399–1401 providing similar outcomes to those observed among non-haemophiliacs. If recombinant FIX is unavailable, FIX concentrate is preferable to PCC, which carries thrombotic risks.1341

Two systematic reviews of thrombotic adverse events1402 and non-thrombotic, non-inhibitor-associated adverse reactions1403 to factor FVIII/FIX concentrates used for treatment of haemophilia and VWD confirm these products’ high degree of safety. Over a 20 year period, only 20 thrombotic events (2 major and 18 superficial thrombophlebitis) and 12.3% allergic reactions were identified, respectively. No differences were reported between the plasma-derived and recombinant products in the incidence of these events.

Recommendation
We suggest that coagulation factors should be given perioperatively by continuous infusion. 2C

Continuous infusion of replacement factors may reduce ‘wasteful’ peaks followed by subtherapeutic concentrations, compared with bolus infusion.1404 For severe haemophilia A patients undergoing surgery, continuous infusion has been shown to reduce FVIII dosage by 36% compared with bolus infusion, while reducing major bleeding complications to zero (compared with a 17% incidence in patients receiving bolus infusion; P = 0.06). The efficacy of continuous infusion has been confirmed in other studies.1405–1407 The first study designed to obtain regulatory approval for continuous infusion of a FVIII product showed similar surgical bleeding in severe haemophilia patients compared with non-haemophilia control patients.1408 Increased risk of inhibitor development has been linked with continuous infusion,1409 but other data do not confirm this risk.1410

Continuous infusion is used in nearly half of patients undergoing major orthopaedic surgery, a greater proportion than suggested by the literature.1379 In a cross-sectional study performed in 22 European centres including 742 patients, continuous infusion was haemostatically very effective (median incidence of postoperative bleeding 1.8%) without increasing the risk of inhibitor development.1411 Half of the centres aimed to maintain high FVIII levels of >0.8–1.0 IU ml⁻¹ during the early postoperative period, employing an initial infusion rate of 4.0–5.0 IU kg⁻¹ h⁻¹. Despite the high target concentration, the impact of continuous infusion on overall cost was favourable.

Continuous infusion of FIX has also been associated with excellent haemostasis and safety.1412–1414

Recommendation
We suggest treatment with either rFVIIa or activated PCCs for haemophilia patients with inhibitors, 2C

Bleeding in haemophilia patients with inhibitors is usually treated with bypassing agents such as PCC (either activated, which can produce thrombin without any requirement for FVIII, or non-activated) or rFVIIa.1415,1416 Large quantities of human factor concentrates or porcine products and plasmapheresis are other options to overcome the inhibitors.1341

A systematic review found that high-dose FVIII was highly successful (100%) in patients with low-titre, low-responding inhibitors undergoing surgery, although not reliable for high-responding inhibitors.1417 Porcine FVIII was effective for controlling bleeding in 60–90% of perioperative bleeding in patients with high-titre or high-responding inhibitors. No evidence supported PCC use in surgery, while APCs controlled approximately 90% of surgical bleeding episodes. rFVIIa controlled 60–100% of surgical bleeding episodes in patients with high-responding inhibitors; results were better when rFVIIa was used early.

In a post-marketing surveillance study of patients with inhibitors, an APCC (FVIII inhibitor bypassing activity [FEIBA]) showed efficacy of 82% and 91% in acute and surgical treatments, respectively.1035 Additionally, prophylactic treatment improved or stabilised clinical orthopaedic status in 11/13 patients (85%). With a small number of adverse events (<0.04%), FEIBA was judged to be safe. No thrombotic complications were reported. Further studies have since confirmed the efficacy of APCC.1036,1038,1418–1421

The dose varied between 50 and 100 IU kg⁻¹ given before surgery and thereafter at 6–12-h intervals,
adjusted to an approximate maximum of 200 IU kg\(^{-1}\) day\(^{-1}\) and tapered when postoperative haemostasis and wound healing permitted. In one study, the median perioperative dose was 130 IU kg\(^{-1}\) day\(^{-1}\) over 12 days for major surgical procedures and 87.5 IU kg\(^{-1}\) day\(^{-1}\) over 2 days for minor procedures.\(^{1038}\) Haemostatic outcome was excellent or good in 78% and 100% of cases, respectively.

In a recent review, good efficacy was reported for rFVIIa in haemophilia patients with inhibitors; rare instances of insufficient haemostasis were attributed to inadequate rFVIIa dosing.\(^{1422}\) In RCT, a high–dose rFVIIa regimen (bolus dose of 90 µg kg\(^{-1}\), followed by a 90 µg kg\(^{-1}\) dose every 2 h for 48 h and then at 4–6 h intervals for 24 h) resulted in fewer postoperative bleeds and fewer extra doses needed than a lower dose regimen (35 µg kg\(^{-1}\) at the same hourly intervals).\(^{1423}\) Recently, a consensus protocol for the use of rFVIIa in orthopaedic surgery in haemophilia patients with inhibitors recommended an initial bolus of 120–180 µg kg\(^{-1}\), followed by a 90 µg kg\(^{-1}\) dose every 2 h for 48 h. Thereafter, the intervals may be increased to 3 h for another 48 h; at day 5 after surgery, the intervals may be further increased to 4 h for the next 3 days followed by further lengthening to 6 h until discharge.\(^{1427}\) Adjunctive tranexamic acid is highly recommended.

An updated evaluation of rFVIIa in perioperative bleeding in patients with inhibitors reported an overall effectiveness of 84% and an incidence of thrombotic events of 0.4%.\(^{1424}\) The efficacy of continuous infusion of rFVIIa is controversial. In an open-label randomised study, 90 µg kg\(^{-1}\) rFVIIa bolus infusion (initially every 2 h) was compared with continuous infusion (initially 50 µg kg\(^{-1}\) h\(^{-1}\)) in inhibitor-expressing haemophilia A/B patients undergoing surgery.\(^{1425}\) Haemostatic efficacy was comparable between the groups, with efficacy demonstrated in 8/11 (73%) and 9/12 (75%) subjects in the bolus infusion and continuous infusion groups, respectively. Cumulative 72-h doses were 237.5 and 292.2 mg, respectively. One patient in the bolus infusion group developed venous thrombosis on day 10 after surgery. Better efficacy has been reported by others using rFVIIa continuous infusion.\(^{1426,1427}\) However, most of these patients also received tranexamic acid.

The relative effectiveness of rFVIIa and APCC for the treatment of acute bleeding in haemophilia patients with inhibitors was investigated by a Cochrane review.\(^{1415}\) Similar haemostatic effects for rFVIIa and APCC were reported, without increasing thromboembolic risk. In the absence of comparative studies carried out in the surgical setting, personal experience, availability and cost may guide the choice of the bypassing agents.\(^{1033}\)

The use of bypassing agents has a substantial economic impact. rFVIIa appears to be at least cost-neutral relative to APCC for mild/moderate bleeding in this patient population.\(^{1428}\) In addition, orthopaedic surgery with rFVIIa in haemophilia patients with inhibitors is generally cost-saving, relative to not having surgery.\(^{1429}\) However, a cost-minimisation analysis for major orthopaedic procedures showed that APCC, alone or alongside rFVIIa, represents a cost-saving approach.\(^{1032}\)

Some haemophilia patients with inhibitors may become refractory to rFVIIa or APCC therapy. Management of these patients is difficult. In a retrospective review, combined therapy with both agents was described.\(^{1430}\) Continuous infusion of low-dose rFVIIa (30–70 µg kg\(^{-1}\)) and low-dose FEIBA (20–30 U kg\(^{-1}\)) appears safe, efficacious and economical in patients refractory to rFVIIa.\(^{1431}\) However, a critical review of 17 reports regarding parallel use of bypassing agents in the same bleeding episode in 49 patients pointed to an increased risk of thrombosis in these patients.\(^{130}\)

Potential thromboembolic risks associated with rFVIIa and APCC have been discussed.\(^{1031,1432}\) However, the methodology of a pharmacovigilance programme suggesting a higher frequency of thrombotic events with rFVIIa over APCC has been criticised.\(^{1031}\) A review article reported 3.67 thromboembolic events per 100 000 rFVIIa infusions in haemophilia patients,\(^{1433}\) comparable to figures reported for FEIBA.\(^{1424}\) Both rFVIIa\(^{1416}\) and APCC\(^{1242}\) administration in haemophilia patients with inhibitors is therefore considered safe.

**Recommendation**

*We suggest the use of antifibrinolytic drugs as perioperative adjunct therapy in haemophilia patients.*

**2C**

In Europe, tranexamic acid is frequently reported as perioperative adjunct therapy in haemophilia patients.\(^{1379}\) Despite frequent use of tranexamic acid, limited evidence supports its coadministration with FVIII.\(^{1434}\) A retrospective survey indicated that tranexamic acid used alongside coagulation factor replacement reduces blood loss after orthopaedic surgery compared with coagulation factor substitution alone.\(^{1407}\) In addition, adjuvant EACA may help to control bleeding in haemophilia patients with inhibitors.\(^{1435}\)

Antifibrinolytic drugs are not recommended for treatment of patients with FIX deficiency already receiving large doses of PCCs.\(^{1307}\)

The antifibrinolytics are particularly indicated in dental care, where the high fibrinolytic activity of saliva may more easily destabilise the relatively weak clot.\(^{1435}\) WFH recommends that EACA or tranexamic acid should be started before replacement therapy. The dose of EACA, which should be started the night before or on the morning of the procedure, is 50–100 mg kg\(^{-1}\) every 4–6 h for 5–10 days (maximum 24 g per 24 h). The dose for tranexamic acid is 25–50 mg kg\(^{-1}\) orally every 6–8 h.
for 10 days. A liquid preparation of these drugs may be used as a mouthwash.\textsuperscript{1387}

A small double-blind cross-over randomised controlled pilot trial including 16 patients with haemophilia showed that tranexamic acid mouthwash was as effective as factor replacement therapy prior to dental scaling.\textsuperscript{1436} Another study including 113 dental extractions in 50 patients with inherited bleeding disorders performed without previous administration of clotting factor concentrates showed that no severe bleeding complications occurred during the follow-up period of 8 days.\textsuperscript{1437}

**Recommendation**

We suggest individualised perioperative thromboprophylaxis in haemophilia patients.\textsuperscript{2C}

When perioperative factor substitution is adequate, the risk of venous thrombosis might be considered. A small prospective study including 24 haemophilic patients undergoing 29 major orthopaedic surgical procedures and screened for VTE by compression ultrasonography showed that subclinical DVT occurred in up to 10\% of cases.\textsuperscript{1438} No case of clinical DVT or PE was reported. Grade 1 compression above-knee stockings were used in all patients. Based on these findings, routine pharmacological thromboprophylaxis may not be indicated in all haemophilic patients undergoing major orthopaedic surgery. However, half of the comprehensive haemophilia centres in Europe reported using pharmacological antithrombotic prophylaxis after major orthopaedic surgery\textsuperscript{1379} and one centre reported that 82\% of haemophiliacs received VTE prophylaxis after the year 2000 with no evidence of increased bleeding complications.\textsuperscript{1381} In a study of open heart surgery in haemophilia patients, individualised antithrombotic measures were reported.\textsuperscript{1439} Individualised antithrombotic therapy, based on local clinical experience, guidelines for non-haemophilia patients and the patient’s clinical characteristics is recommended.\textsuperscript{1440}

### 10.2.4 Rare bleeding disorders

Rare bleeding disorders (RBDs; congenital coagulation factor deficiencies)\textsuperscript{1341} have low prevalence: between 1\%500 000 and 1\%2 000 000.\textsuperscript{1365,1441} They account for 3\–5\% of inherited coagulation disorders,\textsuperscript{1442} and FVII deficiency is the most common.

**Recommendations**

We recommend that patients with rare bleeding disorders should be referred preoperatively to a haematologist for assessment/intervention.\textsuperscript{1C}

Bleeding risk in RBD patients is largely assessed using case reports and expert opinion.\textsuperscript{1365,1441,1442} Minimum required coagulation factors concentrations are controversial\textsuperscript{1443} and correlations between factor concentrations and bleeding risk are generally poor.\textsuperscript{1441,1442}

A retrospective survey in patients with hypo- or afibrinogenaemia reported the mean incidence of bleeding episodes in patients receiving prophylaxis to be not much lower than for patients treated on-demand.\textsuperscript{1444} Unfortunately, no data were reported describing plasma concentrations of fibrinogen at the time of intracranial bleeding.

Risk of bleeding after surgery in patients with FXI deficiency is particularly high if anatomical sites rich in fibrinolytic activity are involved.\textsuperscript{1445} However, among FXI-deficient women giving birth, 69.4\% experienced no postpartum haemorrhage, suggesting no relationship between FXI level and risk of postpartum haemorrhage.

**Recommendations**

We recommend that surgery in patients with rare bleeding disorders should be carried out in consultation with a haematologist with experience in factor deficiencies.\textsuperscript{1C}

There is insufficient data to recommend routine perioperative supplementation of deficient factors in patients with rare bleeding disorders.\textsuperscript{C}

Perioperative bleeding in patients with RBDs is treated by supplementing the deficient factor.\textsuperscript{1446} Coagulation factor supplementation is generally advisable for fibrinogen concentrations <1 g l\textsuperscript{-1} and <20–30\% of normal concentrations for other coagulation factors.\textsuperscript{1447,1359} Thrombosis is a major concern with coagulation factor supplementation; thrombotic events have been reported following administration of fibrinogen and FXI concentrate.\textsuperscript{1365,1441,1442}

The best treatment options, doses and management approaches for patients with RBDs were reviewed in 2004.\textsuperscript{1446} Evidence levels were low (descriptive studies and expert opinion). Treatment is generally administered on-demand, so data on preoperative prophylactic therapy are scarce. UK guidelines recommend specific factor concentrates for fibrinogen and FXIII deficiencies.\textsuperscript{1341}

An open, uncontrolled, retrospective study showed that fibrinogen concentrate was effective as preoperative prophylaxis.\textsuperscript{1446} However, one high-risk patient developed DVT and non-fatal pulmonary embolism; fibrinogen substitution could not be excluded as a contributing factor.

Another open-label, uncontrolled, prospective study of patients with afibrinogenaemia showed that human fibrinogen concentrate can restore haemostasis with a good safety profile.\textsuperscript{1354}

Supplementation is not always necessary in FVII deficiency. In a retrospective analysis of surgical procedures performed without replacement therapy in FVII-deficient patients, the median FVII level was 5\% and the bleeding rate was 15\%.\textsuperscript{1449} A threshold level for FVII replacement of 10\% was proposed.

FFP (preferably virally inactivated) is the only current option for FV deficiency, and other deficiencies if the
concentrates are not available; non-virally inactivated cryoprecipitate may be an option for minimising administration volume. PCCs are recommended for FII or FX deficiencies, because specific concentrates are not available. Evidence supporting prophylactic use of PCCs in prothrombin or FX deficiency is scarce. rFX and rFXIII are currently being developed. Phase I data suggest that rFXIII may be safe and effective in patients with FXIII deficiency.

For FXI deficiency, both FXI concentrate and virally inactivated FFP are reasonable, although tranexamic acid alone may suffice for minor procedures. However, there is evidence that prophylactic treatment is not mandatory in FXI deficiency.

Vitamin K is the mainstay treatment for vitamin K-dependent clotting factor deficiency. However, perioperative supplementation using plasma or PCC may also be needed.

**Recommendations**

*We suggest that rFVIIa should be used in perioperative bleeding due to inherited FVII deficiency. 2C*

If rFVIIa is given to control perioperative bleeding in inherited FVII deficiency, we suggest lower doses than in haemophilia patients. 2C

*There are insufficient data to recommend rFVIIa in perioperative bleeding for patients with other rare bleeding disorders. C*

rFVIIa is the treatment of choice for FVII deficiency. If rFVIIa is not available, plasma-derived FVII is favoured over PCC because of PCC’s potential thrombogenicity. A wide rFVIIa dose range (1.2–223.8 μg kg⁻¹) has been reported in FVII deficiency. Dosing intervals of 2–18 h and treatment durations of 30 h to 2 weeks are described. Continuous infusion of rFVIIa has also been reported in FVII deficiency.

The recommended dose of rFVIIa for FVII deficiency is 20–25 μg kg⁻¹ every 4–6 h, individualised according to bleeding phenotype. In surgery, the specific procedure, tissue/organ involved and type of anaesthesia should be taken into account. Supplementation is recommended until wound healing is established (5–7 days).

In a prospective study of subjects with FVII deficiency undergoing surgery, rFVIIa (≥3 doses of ≥13 μg kg⁻¹) proved effective. Bleeding occurred in three patients to whom rFVIIa was given at low doses. FVII antibody was observed in one patient undergoing a multiple dental extraction. No thromboses were reported. Low-dose rFVIIa (33–47 μg kg⁻¹) also appears safe and effective for surgery in patients with severe FXI deficiency and inhibitors. Co-administration of tranexamic acid has also proved effective, although it may increase thrombotic risks.

Elsewhere, effective haemostasis was reported in 100% of FVII-deficient patients receiving prophylactic rFVIIa before dental procedures or minor and major operations. No alternative haemostatic agents or transfusions were administered, except for tranexamic acid. An acute cerebrovascular accident was reported in a patient with a history of cardiovascular disease. The authors concluded that rFVIIa was an effective alternative to plasma-derived FXI, but that rFVIIa may not be suitable for patients with pre-existing thrombotic risk factors.

rFVIIa appears effective in patients with FV or FVIII deficiency and surgical bleeding resistant to supplementation therapy. Registry data suggest that rFVIIa treatment may control or prevent bleeding in other RBDs, with a favourable safety profile.

**Recommendation**

*There are insufficient data to recommend periprocedural desmopressin or antifibrinolytic drugs in patients with mild rare bleeding disorders. C*

Desmopressin has also been used in RBDs, especially mild cases. Limited data suggest a potential role for desmopressin in the treatment of bleeding episodes or prevention of postoperative bleeding in mild FXI defects. Such use is described in a systematic review of 16 case reports.

Antifibrinolytic agents may be given to patients with RBDs, particularly for mucosal bleeding or bleeding prevention following dental extractions.

**11 FINAL REMARKS**

The overall aim of this extensive document is to provide clinicians with evidence-based and up-to-date guidelines for better clinical management of our patients. Great care has been taken by the task force and the steering committee to follow a transparent and comprehensive approach in finding relevant literature and assessing the existing evidence.

Guided by expert assistance, our search strategy was based on predefined criteria and broadly adhered to accepted methodologies, such as those advocated by the Cochrane Collaboration. More than 20 000 abstracts were selected by a sensitive search strategy. As with all database searches, it is possible that some relevant literature was not initially captured. Therefore, to make the process as robust as possible, the authors of each section were asked to conduct supplementary searches and provide the committee with any additional relevant literature. The authors subsequently assessed all publications relevant to their sections.

As initially required by the ESA Scientific and Guideline committee, we applied the SIGN method, which places emphasis on risk of bias when grading the quality of the evidence in publications such as systematic reviews or RCTs. This approach is similar to that advocated by the
Cochrane Collaboration for evaluating the quality of trials and the various domains of bias. When assessing all relevant publications, the authors were required to consider important issues such as publication bias, inconsistency, indirectness, imprecision and funding bias. Finally, the authors were requested to combine the above with their own expert opinions in a transparent manner to generate appropriate and clinically meaningful recommendations.

The team of authors acknowledges that, despite adhering to common assessment tools such as SIGN and GRADE, it is nearly impossible when creating a guideline to avoid an element of subjectivity. Indeed, these guideline tools provide room for subjectivity, for instance when weighing risks versus benefits, considering preferences of patients and evaluating resources and costs. Despite the universal acceptance of its importance, evidence-based medicine is an ideal that is often very difficult to achieve. If guidelines had to be developed using a purely objective approach with no room for subjectivity, we would be left with very little of true value to recommend. Thus, guidelines per se will always be subject to a degree of subjectivity. What is essential is that readers are provided with sufficient information to assess the degree of transparency of the process by which a guideline has been developed. We believe that we have achieved this in this detailed document.

It comes as no surprise that there are variations in our practices across Europe. We acknowledge the importance of guidelines as a steering tool but also appreciate the fact that recommendations should be evaluated locally. Some countries and national societies may decide to assess the evidence and recommendations differently.

Some institutions may decide not to introduce devices, medications or strategies advocated in this guideline until further supporting evidence is available. This might be the case with point-of-care testing and products such as fibrinogen concentrate and prothrombin complex concentrate, for which the results of the many ongoing trials are eagerly anticipated.

Furthermore, some institutions may consider it difficult to justify funding the introduction, daily use and maintenance of point-of-care devices, and the higher direct costs of coagulation factor concentrates compared with allogeneic blood products. We note, however, that although allogeneic blood products are perceived as low cost, substantial indirect and infrastructure costs mean that the actual cost of transfusion is high. There is evidence that use of coagulation factor concentrates guided by point-of-care testing may actually reduce costs in some settings. However, cost analyses performed in studies will not reflect the local situation in every hospital and prices for allogeneic blood products and coagulation factor concentrates vary among countries depending on the local market. This task force acknowledges these issues and our recommendations may need to be viewed differently in some countries and institutions until additional evidence to support routine use of these products and devices is published. This statement is in accordance with the official position of the ESA Guideline Committee, and we emphasise that our recommendations can be adopted, modified or not implemented, depending on institutional or national requirements.

Many of the authors and experts involved in developing this guideline have conflicts of interest. Each of these individuals has provided a detailed disclosure statement, as declared in this article. In order to minimise bias in our assessment of the literature, the entire guideline document was subject to internal and external review and was open to critical input from colleagues and national organisations.

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How do you treat bleeding disorders with desmopressin?

Bülent Özgonenel, Madhvi Rajpurkar, Jeanne M Lusher

Desmopressin is one of the several non-transfusional pharmacological agents within the clinician’s armamentarium for treating bleeding episodes, which include, among others, anti-fibrinolytic agents tranexamic acid, e-amino-caproic acid and aprotinin; recombinant human factor VIIa; and the conjugated oestrogens. Its properties of ease of use, low cost and versatility in preventing and treating bleeding from various sites of the body in a variety of bleeding disorders make it a useful haemostatic drug. Importantly, it carries no risk of transmitting bloodborne infectious agents. Since its introduction into clinical use in 1977, it has revolutionised the treatment of bleeding disorders, leading to a marked reduction in the use of blood products for the prevention and treatment of bleeding episodes.

This review outlines the basic knowledge on desmopressin, and attempts to reintroduce it to the primary care clinician, who could be an emergency room physician treating epistaxis in a patient with mild haemophilia A, a nurse practitioner treating gum bleeding in a patient with end-stage renal disease, a dentist anticipating wisdom tooth extraction in a patient with type 1 von Willebrand disease (VWD), or a paediatrician treating a female adolescent patient with type 1 VWD experiencing excessive menstrual bleeding. In these clinical scenarios, understanding the pathogenesis of the disease process and the mechanism of action of desmopressin will enable the clinician to formulate a plan of action for the patient in conjunction with the haematologist and avoid delay in patient management.

PHYSIOLOGY OF THE VON WILLEBRAND FACTOR

Insight into the normal and pathological physiology of the von Willebrand factor (VWF) will facilitate understanding of the mechanism of action of desmopressin. Both the factor and the disease are named after Dr Erik von Willebrand, a Finnish physician who, in 1926, first described a hereditary haemorrhagic disease with autosomal dominant inheritance pattern in a large kindred from the western coast of Finland. His index patient was a young girl who died of menstrual haemorrhage soon after her menarche, clearly epitomising the involvement of females in this bleeding disorder as opposed to that in haemophilia A or B. It was only years later, well into the late 20th century, that it was appreciated that the disease originated from a quantitative or qualitative deficiency of a plasma protein of high importance in the normal haemostatic mechanism.

VWF is a complex multimeric glycoprotein with two important roles in haemostasis: it binds to platelet receptors, bridging them to other platelets and subendothelial tissue that is exposed after vascular injury, and also acts as a carrier protein for the coagulation factor VIII (FVIII), thus preventing its proteolytic inactivation in the plasma. Without the VWF, FVIII plasma levels decline rapidly; and depending on the severity of the disorder, a haemostatic defect similar to haemophilia A emerges.

The gene for VWF is located on chromosome 12. During its synthesis in endothelial cells and megakaryocytes, VWF undergoes extensive processing in the Golgi apparatus of these cells, including polymerisation into a large molecule with a molecular weight of 20 000 kDa. Stored inside specialised storage organelles, the Weibel–Palade bodies of endothelial cells and α-granules of platelets, VWF is released into circulation both constitutively and on stimulation. Myriad substances act as secretagogues of the VWF, including histamine, thrombin, epinephrine and vasopressin.

VWF is released into plasma as a large multimer, which is instantaneously broken down by a protease into several molecules of varying molecular sizes: multimers with high, intermediate and low molecular weight. The protease that cleaves VWF immediately on its release into the plasma, ADAMTS13, has recently gained clinical relevance when it was understood that its deficiency underlies the pathogenesis of thrombotic thrombocytopenic purpura. In this disorder, platelet aggregation occurs around the unusually large VWF molecules in circulation, leading to disseminated thrombosis and multiorgan dysfunction.

The high-molecular-weight multimers, by virtue of their strong affinity to platelet receptors, are considered more potent than the other multimers.

Abbreviations: FVIII, coagulation factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor
The absence of these multimers leads to a defect in platelet adhesion, prolonging the bleeding time. Ristocetin is an antibiotic that enhances the interaction between the VWF and the platelet receptors. On the basis of this effect, ristocetin cofactor activity test is used as a surrogate marker of the functional activity of the VWF. Box 1 summarises the physiology of VWF.

MECHANISM OF ACTION OF DESMOPRESSIN
Vasopressin is a secretagogue of VWF. This hormone functions through two receptors, termed V1 and V2, which activate different intracellular second messengers. Agonist activity at V2 receptors leads to a rise in intracellular concentrations of cyclic adenosine monophosphate, which in turn induces exocytosis of VWF from its storage sites (ie, Weibel–Palade bodies of endothelial cells) into the circulation. Interestingly, tissue plasminogen activator, a molecule involved in fibrinolysis and therefore in opposition to the effects of VWF, is also released into circulation along with VWF. Desmopressin (1-desamino-8-arginine vasopressin, also abbreviated DDAVP) is a synthetic analogue of vasopressin, which activates only V2 receptors and thus lacks its vasococonstrictor and uteoretic properties. Intravenous or intranasal administration of desmopressin to healthy individuals is followed by a rise in levels of both VWF and its precious cargo, FVIII. Individuals who lack V2 receptors—that is, patients with nephrogenic diabetes insipidus—are expected to do not show this increase in VWF and FVIII levels.

Although originally designed for the treatment of diabetes insipidus, desmopressin emerged as a haemostatic agent, with the appreciation of its effects on coagulation and the lack of the severe side effects associated with vasopressin. The next section discusses the bleeding disorders amenable to treatment with this drug.

BLEEDING DISORDERS TREATED WITH DESMOPRESSIN
von Willebrand disease
von Willebrand disease (VWD) is categorised into three major types. Mild quantitative deficiency of VWF molecule with a normal multimer pattern is the cause of type 1 VWD, the most common inherited bleeding disorder, affecting up to 1% of the population. Total or near-total absence of VWF leads to type 3 VWD, which is the most severe but fortunately a rare type. Understandably, desmopressin is a useful therapeutic agent in type 1 VWD, where there is residual VWF in the endothelial storage sites to provide haemostasis, at least temporarily.

Owing to presence of little or no VWF in the storage sites in type 3 VWD, desmopressin shows no therapeutic benefit in this disease. Type 2 VWD is characterised by a qualitative defect in the VWF molecule. Some patients with type 2 VWD will show absence of the high-molecular-weight multimers (types 2A and 2B). Type 2B is characterised by a gain-of-function type of interaction between platelets and VWF, leading to spontaneous platelet aggregation and thrombocytopenia due to clearance of the platelet–VWF complexes from circulation. Other patients with type 2 VWD will have a normal multimer pattern, but laboratory evaluation will detect either a deficient interaction with the platelet receptors (type 2M) or a deficient FVIII-carrying activity (type 2N). Type 2N is characterised by rapid proteolysis of FVIII, and the clinical picture is much like that of haemophilia A. Theoretically, desmopressin is not expected to provide any haemostatic effect in type 2 VWD, because the VWF released from the storage sites will still be abnormal. Surprisingly, however, some patients with type 2 VWD will have a laboratory and clinical response to desmopressin. Notably, type 2B constitutes a theoretical contraindication to the use of desmopressin, as the release of abnormal VWF molecules with a gain-of-function defect is expected to trigger spontaneous platelet aggregation and thrombocytopenia. Table 1 shows a synopsis of the types of VWD and the response to desmopressin in individual types.

Haemophilia A
FVIII has a critical role in the coagulation cascade by acting as a cofactor for factor IXa in the activation of factor X, the common-pathway protease that will subsequently activate thrombin, the real propeller of the coagulation machine. In the absence of FVIII, the activation of factor X is sluggish, leading to an intolerable delay in coagulation. Many different mutations of the FVIII gene on the X chromosome, but most commonly inversion of one of the introns of the FVIII gene, disrupt the synthesis of the product molecule. Patients with such mutations have no detectable levels of FVIII, and are clinically at the most severe end of the spectrum, exhibiting potentially crippling or fatal, spontaneous bleeding episodes. Unfortunately, these patients do not benefit from administration of desmopressin, because increases in plasma levels of VWF alone without its precious cargo, the FVIII molecule, will not translate into a haemostatic effect. Some patients with haemophilia A, however, have detectable FVIII levels because a single nucleotide substitution in the FVIII gene will still allow the translation of a mutant FVIII molecule, albeit with diminished factor activity. These patients are classified into the category of mild or moderate haemophilia, and may fortunately respond to desmopressin.

Other bleeding disorders
Various acquired or inherited disorders of bleeding have been documented to respond to desmopressin. The exact mechanism underlying this therapeutic effect is not known but may be related to several events associated with the release of VWF. First of all, sheer increase in FVIII levels will accelerate the activation of factor X, thus providing a faster coagulation. Secondly, unlike its constitutive release into the lumen of vessels, stimulated release of VWF is thought to occur on the abluminal surface of the endothelial cell, directly bringing VWF into contact with the subendothelial tissues. This may in turn provide a more efficient platelet adhesion, a process that is possible only through interaction between platelets and VWF. Finally, desmopressin induces the release of the unusually large VWF molecules, which are more adhesive than the regular-sized VWF molecules in circulation.
USE OF DESMOPRESSIN IN THE TREATMENT OF BLEEDING DISORDERS

Desmopressin has been successfully used in the prophylaxis and treatment of bleeding episodes in some patients with VWD types 1 and 2, mild to moderate haemophilia A, platelet function defects related to aspirin use, uraemia and inherited platelet disorders, bleeding related to cirrhosis (excluding acute gastrointestinal bleeding), or heparin use.1,16 Patients with inherited disorders should undergo a trial to document an improvement in laboratory parameters, which could be an increase in VWF and ristocetin cofactor activity levels for patients with VWD, increase in FVIII levels for patients with haemophilia A, and normalisation of bleeding time or platelet function analysis test for patients with inherited platelet disorders. Before starting treatment, it is important to inquire about response to desmopressin trial, and the patient’s haematologist should be contacted if in doubt. The haematologist should definitely be consulted for the management of a patient with bleeding disorders who has never used desmopressin before.

Desmopressin can raise VWF and FVIII levels by 3–5-fold. As the response to desmopressin in an individual patient is consistent on different occasions, knowledge of the expected response and baseline levels of factor is essential to determine the optimal mode of treatment. For example, for a patient with haemophilia with baseline FVIII levels of 10% that responds to desmopressin by a fourfold increase, a combination of desmopressin and oral antifibrinolytics could be sufficient prophylaxis before a simple dental extraction. The same patient would need to be treated with FVIII concentrates for the treatment of a limb or life-threatening haemorrhage, or in preparation for major surgery.

The efficacy of desmopressin in preventing or treating menorrhagia in patients with bleeding disorders is not clear because of conflicting results from studies in which desmopressin was used in the treatment of menorrhagia in women with VWD.14 Desmopressin paradoxically causes release of the tissue plasminogen activator, a fibrinolytic substance, along with the VWF, and thus may actually increase menstrual bleeding. A therapeutic trial can be undertaken for each individual woman to gauge the clinical response, as a guide for future plan of action. Pictorial chart assessment can be used to estimate menstrual blood loss. It is important to exclude other causes of menorrhagia, such as dysfunctional uterine bleeding, before the use of haemostatic agents.

Both intranasal and subcutaneous desmopressin was found to be effective in the treatment of menorrhagia in women with VWD.14-16 Unfortunately, the optimal dosing schedule to prevent menstrual bleeding is not known, although a tentative approach would be a dose at the onset of menses followed by two subsequent doses every 24 h.15 Alternative treatment strategies would include oral tranexamic acid, oral contraceptives, levonorgesterel-releasing intrauterine systems and endometrial ablations.17

DOSGING AND ADMINISTRATION

Desmopressin can be given through intravenous, subcutaneous and intranasal routes. The dose for both intravenous and subcutaneous routes is 0.3 μg/kg. When giving intravenously, the drug is diluted in normal saline and infused over 15–30 min. The dilution volume of normal saline is 15–30 ml for children and 50–100 ml for adults. The intranasal dose is 150 μg for patients weighing <50 kg (one puff into one nostril) and 300 μg for patients weighing ≥50 kg (one puff into each nostril). The intranasal solution of desmopressin used in the treatment of bleeding disorders (Stimate, Ferring AB, Limhamn, Sweden) is more concentrated than that used in the treatment of nocturnal enuresis or diabetes insipidus. The peak effect is achieved 30–60 min after intravenous infusion, and 60–90 min after an intranasal or subcutaneous dose. This timing should be taken into account when desmopressin is given as prophylaxis before procedures. Owing to the shorter time required to achieve the haemostatic effect, intravenous route is preferred to subcutaneous and intranasal routes when treating acute bleeding episodes. High levels of FVIII and VWF are maintained for 6–8 h.1-10 Table 2 provides a summary of dosing of desmopressin.

The dose can be repeated every 12–24 h depending on the type and severity of bleeding; however, most patients with moderate haemophilia A (and to a lesser extent, those with VWD) respond less with each consecutive dose (tachyphylaxis) because of exhaustion of VWF stores. Therefore, to achieve longlasting haemostasis during recovery from major trauma or surgery, specific factor concentrates or platelet transfusions should be provided, depending on the underlying disease.

The response to desmopressin can be monitored using laboratory tests specific for the bleeding disorder. Platelet function analyzer PFA-100 (Dade International, Miami, Florida, USA), which has been introduced as an alternative to bleeding time, is a new in vitro tool to test platelet function globally. The results are given as closure times representing formation of a platelet aggregate within its two cartridges that contain either adenosine diphosphate or epinephrine, agonists for platelet activation.14 PFA-100 may be a be a useful adjunct to monitor response to desmopressin in patients with type 1

Table 2 Doses and preparations of desmopressin

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Dose and preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>Stimate 150 μg for body weight &lt;50 kg (one spray into one nostril) 300 μg for body weight ≥50 kg (one spray into each nostril)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.3 μg/kg body weight diluted in normal saline (15–30 ml for children, 50–100 ml for adults) and given over 15–30 min</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>0.3 μg/kg body weight</td>
</tr>
</tbody>
</table>

Table 1 Desmopressin use in various types of von Willebrand disease

<table>
<thead>
<tr>
<th>Type of VWD</th>
<th>Characteristic features</th>
<th>Desmopressin use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Mild to moderate decrease in plasma VWF levels with a normal multimer pattern</td>
<td>Trial needed before use</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Absence of multimers with high and intermediate molecular weight</td>
<td>Trial needed before use</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Increased affinity for platelet receptors, ultimately leading to excessive platelet activation and thrombocytopenia</td>
<td>Trial needed before use</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Mutation in the region of the VWF that binds to platelet receptors, disrupting platelet adhesion</td>
<td>Trial needed before use</td>
</tr>
<tr>
<td>Type 2N</td>
<td>Undetectable levels of the VWF with severe bleeding diathesis</td>
<td>Not useful</td>
</tr>
<tr>
<td>Type 3</td>
<td>Undetectable levels of the VWF</td>
<td>Trial needed before use</td>
</tr>
</tbody>
</table>

VIII, coagulation factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.
As PFA-100 is an expensive test and knowledge regarding its utility in monitoring haemostasis is yet evolving, at the time of writing this manuscript, the general practitioner is advised only to become familiar with the interpretation of its results but not to use it as a routine test to monitor response to desmopressin.

**ADVERSE EFFECTS, PRECAUTIONS, AND CONTRAINDICATIONS**

The most common side effects encountered with the use of desmopressin are tachycardia (mild), flushing and headache (mild). As desmopressin is a potent anti-diuretic agent, it can cause hypotension and even seizures in patients receiving generous amounts of hypotonic intravenous or oral fluids, necessitating fluid restriction during desmopressin treatment. This fact is especially important in the context of treatment of minor bleeding episodes at home, and the patients or care givers should be instructed to observe fluid restriction after giving desmopressin. For young children who are inpatients (ie, postoperative patients), hypotonic intravenous fluids should be avoided and total fluid intake should be reduced to 75% of maintenance requirements in the 24 h after use of desmopressin. Monitoring serum sodium levels and osmolality before and after desmopressin use would be prudent in young children, especially if more than one dose is used over a 24-h period.

A rare but serious side effect in patients receiving desmopressin is the occurrence of arterial thrombotic events, such as stroke or acute myocardial infarction. Caution should be exercised, therefore, with the use of desmopressin in elderly patients with atherosclerotic disease. Venous thrombosis is likewise rare after desmopressin administration, and has been observed only in patients who had received desmopressin after transfusion of FVIII/VWF concentrates. Patients with thrombocytopenic purpura should not receive desmopressin because further release of the unusually large VWF molecules into plasma is thought to add more fuel to the ongoing thrombotic event in these patients. Thrombocytopenia can easily develop in patients with type 2B VWD after desmopressin use, and this disease represents a classic contraindication to the use of desmopressin; however, some patients with type 2B VWD have had a therapeutic response to desmopressin without developing thrombotic complications. Therefore, desmopressin should be used in patients with type 2B VWD only under the guidance of a haematologist.

It is also important to recognise disorders where desmopressin will not be effective, such as type 3 VWD and severe haemophilia A. Recombinant or plasma-derived factor concentrates and other non-transfusional agents, such as conjugated oestrogens or antifibrinolytics, can be helpful in the management of patients with such bleeding problems.

Desmopressin does not provide any haemostatic benefit in severe haemophilia B, deficiency of factor IX. Factor IX and FVIII work together to activate factor X, so artificially increasing the levels of one factor is not expected to compensate for the lack of the other. Nevertheless, response to desmopressin has been reported in patients with mild to moderate haemophilia B, perhaps because of a generalised haemostatic effect. Box 2 summarises the guidelines for the use of desmopressin in bleeding disorders.

**CONCLUSION**

Desmopressin has revolutionised the treatment of bleeding disorders since its introduction to haematology in 1977. The resultant avoidance of blood products has saved numerous lives since then. Intranasal and subcutaneous routes render it convenient for treatment at home, avoiding emergency room or office visits for simple bleeding problems. Clinicians in primary care should familiarise themselves with the indications, dosing, side effects and contraindications of this versatile tool for haemostasis.

### SELF-ASSESSMENT QUESTIONS; ANSWERS AT THE END OF REFERENCES

1. Desmopressin exerts its haemostatic effect by:
   
   A. Inducing synthesis of the von Willebrand factor (VWF) by endothelial cells
   B. Stimulating release of the VWF from its storage sites in endothelial cells
   C. Cleaving the large VWF multimers circulating in plasma into smaller multimers
   D. Enhancing interaction between platelets and the VWF
   E. Binding to VWF receptors on platelets

2. Desmopressin is not expected to show any haemostatic effect in patients with:

   A. Uraemia
   B. Type 1 von Willebrand disease (VWD)
   C. Type 3 VWD
   D. Mild haemophilia A
   E. Platelet function defect secondary to aspirin use

3. A 2-year-old boy with mild haemophilia A, known to be responsive to desmopressin, is hospitalised for elective surgery. He receives a single intravenous dose before and

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**Box 2: Guidelines for the use of desmopressin in bleeding disorders**

- Inquire about response to trial
- Administer 30–60 min before procedure
- Restrict fluid intake
- Monitor serum sodium level and osmolality in young children
- Anticipate tachyphylaxis after repeated doses
- Monitor therapeutic response with an appropriate test for the individual bleeding disorder

**Key references**


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two more doses 12 h apart after surgery, which proceeds without any haemorrhagic complications. To thwart serious side effects of desmopressin, postoperative care should include:

A. Monitoring serum sodium levels
B. Serial electrocardiograms
C. Chest radiograph
D. Prothrombin time and partial thromboplastin time
E. Platelet count

4. A 20-year-old woman (weight 54 kg) with type 1 VWD is going to have wisdom tooth extraction. The appropriate dose and timing for the intranasal solution is:

A. One puff (150 µg) to one nostril 10 min before the procedure
B. One puff to each nostril (total dose 300 µg) 10 min before the procedure
C. One puff (150 µg) to one nostril 60 min before the procedure
D. One puff to each nostril (total dose 300 µg) 60 min before the procedure
E. Two puffs to each nostril (total dose 600 µg) 60 min before the procedure

5. Which of the following is NOT part of the guidelines for the use of desmopressin in children for the treatment of bleeding episodes?

A. Inquiry about response to a previous trial of desmopressin
B. Generous use of intravenous fluids
C. Anticipation of reduced haemostatic effect after repeated doses
D. Monitoring serum sodium and osmolality in patients receiving multiple doses
E. Monitoring the therapeutic response with appropriate tests

Authors' affiliations
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Competing interests: None.

REFERENCES

ANSWERS
1. (B) 2. (C) 3. (A) 4. (D) 5. (B)
Summary. Bleeding disorders, including haemophilia, von Willebrand disease, and platelet function abnormalities pose a substantial, ongoing management challenge. Patients with these disorders not only require treatment during bleeding events but also need effective management strategies to prepare for events ranging from minor dental procedures to major surgery and childbirth. Moreover, women with bleeding disorders often require ongoing treatment to prevent menorrhagia during childbearing years. Desmopressin (DDAVP), a synthetic derivative of the antidiuretic hormone L-arginine vasopressin, has become a well-established tool for the management of patients with bleeding disorders in a variety of clinical settings. However, despite the widespread use of DDAVP, the available clinical evidence on its efficacy and safety in these settings is limited, and there has not been a recent comprehensive review of its role in the clinical management of patients with bleeding disorders. As such, this article provides a review of the mechanism of action and pharmacokinetic properties of DDAVP, followed by a concise summary of the available evidence for its use in the treatment and prevention of bleeding.

Keywords: DDAVP, desmopressin, haemophilia A, von Willebrand disease

Introduction

Exogenously administered desmopressin (DDAVP), a synthetic derivative of the antidiuretic hormone L-arginine vasopressin, raises plasma levels of factor VIII (FVIII) and von Willebrand factor (VWF). The ability of intravenously (IV) administered DDAVP to treat selected patients with haemophilia A and von Willebrand disease (VWD) was first described by Mannucci in 1977 [1]. With the introduction of a high-dose intranasal (IN) formulation in Europe (Minirin® desmopressin acetate; Ferring Pharmaceuticals, Saint-Prex, Switzerland) and the United States (Stimate® desmopressin sulfate; CSL Behring, King of Prussia, PA, USA) over the past two decades, the role of DDAVP further expanded to include its routine use in the home setting, where self-administration facilitates the timely treatment of bleeding episodes. DDAVP use has also been reported to successfully prevent or treat bleeding in patients with other bleeding disorders, including mild platelet function defects and vascular abnormalities such as Ehlers-Danlos syndrome (EDS) [2].

Despite the widespread use of DDAVP, there is a paucity of clinical trial data available to guide treatment, and few comprehensive reviews have been published. The purpose of this article was to conduct a systematic review of the MEDLINE and Embase databases, and concisely summarize data from available peer-reviewed articles pertaining to the efficacy and safety of DDAVP in the management of patients with congenital bleeding disorders. The review was restricted to articles published in English. Studies evaluating both paediatric and adult patient populations were included, and this review includes all relevant articles.
DDAVP mechanism of action and pharmacokinetics

Desmopressin (1-deamino-8-D-arginine vasopressin) acts through antidiuretic type 2 vasopressin receptors and is nearly devoid of activity through type 1 receptors, which reduces undesirable vasoactive side effects and prolongs its half-life when compared to native vasopressin [3–5]. Following DDAVP administration, cyclic adenosine monophosphate signals the secretion of VWF and tissue plasminogen activator (t-PA) from Weibel-Palade bodies in endothelial cells into plasma [2,6]. The released VWF is highly multimerized, which enhances binding to the subendothelial matrix and platelets, and increases haemostatic efficacy [6]. FVIII, which co-localizes with VWF, is also released from storage sites following DDAVP administration. DDAVP-induced increases in plasma VWF may protect FVIII from proteolytic degradation, contributing to additional, sustained increases in FVIII activity [6]. DDAVP-induced release of t-PA briefly increases fibrinolysis, but does not interfere with DDAVP’s overall haemostatic efficacy.

DDAVP increases the expression of glycoprotein Ib/IX and CD62 (P-selectin) on platelet surfaces, leading to increased platelet rolling, activation and adhesion [7,8]. Collectively, these actions can shorten the bleeding time and normalize shear-induced platelet aggregation [2,4,7,9].

DDAVP has a biphasic half-life that contributes to rapid onset of antidiuretic activity. The terminal half-life of DDAVP is 3.5 h in healthy volunteers and increases to 9 h in patients with renal insufficiency; it is primarily excreted in the urine.

DDAVP is currently available in IV, subcutaneous (SC) IN, and oral formulations. The oral formulation of DDAVP has insufficient efficacy in patients with congenital bleeding disorders, so this discussion will focus on the IV, SC and IN routes of administration. IV DDAVP shows peak activity within 30 min of infusion, raising FVIII:C levels twofold to fourfold in patients with bleeding disorders (levels return to baseline 24 h after a single dose) [10]. IV DDAVP also increases VWF activity, but the impact is not as dramatic as it is on FVIII, and there is more inter-patient variability [11]. In studies evaluating the effect of IV DDAVP in patients with congenital or acquired platelet disorders, a specific platelet effect appears within 30 min of administration and dissipates within 3–4 h [12–14].

While the pharmacokinetics of SC-administered DDAVP is similar to that of IV dosing, IN administration is associated with greater variability in absorption, time to peak activity and peak duration of activity [10]. A response is generally seen within 1–4 h after IN dosing, and the duration of activity is typically 6–8 h. Decreased absorption of IN DDAVP can occur in patients with nasal obstruction or allergic rhinitis [15]. Because of this, many prefer the IV formulation for a DDAVP challenge, although IN DDAVP can be suitable in patients who have shown a consistent response to DDAVP in this formulation.

A summary of pharmacokinetic properties of DDAVP by administration route is provided in Table 1.

**Response to DDAVP and challenge testing**

DDAVP is most effective in patients with mild haemophilia A (FVIII:C > 5%) and patients with type 1 VWD who have functionally normal VWF. Overall, about 80–90% of these individuals will have a clinically meaningful haemostatic response to DDAVP [14,16]. Although there is no standard criterion for defining a response, most investigators define a response as a rise in FVIII and VWF of at least twofold to threefold, with FVIII and VWF levels ≥0.3 IU dL⁻¹ 1–2 h after DDAVP administration [16,17]. For patients with rapid VWF-clearance forms of type 1 VWD (i.e. ‘Vincenza’ variants), response to DDAVP may appear to be substantial, with an increase in baseline VWF and FVIII:C levels of fivefold to 10-fold; however, there is a rapid decline in levels, with a terminal half-life as short as 60 min, which may limit its usefulness in such patients for most clinical situations [18]. In addition, in patients with type 2B VWD, VWF levels may increase following DDAVP administration, only to precipitate a worsening of thrombocytopenia [19], leading most clinicians to avoid its use in this type of VWD.

<table>
<thead>
<tr>
<th>Table 1. FVIII and VWF responses resulting from different routes of DDAVP administration.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV</strong></td>
</tr>
<tr>
<td>Standard/recommended <em>dose (VWD)</em></td>
</tr>
<tr>
<td>(given over 30 min)</td>
</tr>
<tr>
<td>Peak activity</td>
</tr>
<tr>
<td>Time to peak activity</td>
</tr>
<tr>
<td>Half-life of haemostatic effect</td>
</tr>
<tr>
<td>Dosing considerations</td>
</tr>
</tbody>
</table>

IV, intravenous; SC, subcutaneous; IN, intranasal; VWD, von Willebrand disease; VWF, von Willebrand factor; FVIII, factor VIII.
DDAVP is not recommended for children under 2 years of age because of decreased responsiveness and increased toxicity; however, children typically become more responsive as they age. In a study of 74 boys with mild or moderate haemophilia A, 10 of 11 who underwent DDAVP challenge testing at a median of 2 years of age had an improved response (i.e. attained higher FVIII:C levels) when retested at a median of 5 years of age. In fact, retesting resulted in nearly half of these patients being reclassified as DDAVP responders [20]. For patients with more severe forms of haemophilia A or VWD, responsiveness to DDAVP is variable (Table 2), and such treatment is not advised [2,31].

A DDAVP challenge test is recommended before first use in patients with haemophilia A or VWD to document response and assess tolerability. For patients with platelet disorders or other congenital bleeding disorders (e.g. EDS), demonstrating a quantitative laboratory response to DDAVP is more difficult. The PFA-100 (Siemens Ag, Deerfield, IL, USA) and the Simplate bleeding time assay (BioMerieux Inc., Durham, NC, USA) have been proposed as laboratory measures to gauge the haemostatic effect of DDAVP in these patients, but their clinical usefulness remains uncertain [14,32,33]. For the majority of patients with mild platelet function disorders, DDAVP is used empirically because there is no reliable laboratory assay to monitor response.

DDAVP dosing

The standard IV or SC dose of DDAVP is 0.3 μg kg⁻¹. Some guidelines suggest a maximum dose of 20 μg to avoid untoward effects [20]; however, such a restriction may lead to a diminished clinical response in patients weighing over 70 kg. In addition, young children tend not to respond as well to DDAVP as do adults, possibly the result of dosing based on body weight rather than surface area [20].

The recommended IN dose of DDAVP is 150 μg (one puff) for patients weighing ≤50 kg, and 300 μg (two puffs) for those weighing >50 kg, which translates to a potential twofold difference in dose for individuals close to the cut-off weight [11]. IN DDAVP has been shown to be equally as effective as the IV formulation in raising VWF and FVIII:C levels [11].

Repeated DDAVP dosing leads to the phenomenon of tachyphylaxis, the loss of therapeutic effect after repeated dosing [4,6]. This development, which is more pronounced in patients with haemophilia A than with VWD [24], relates to depletion of VWF and factor VIII (FVIII).

Table 2. Prospective studies of IV DDAVP and laboratory response by VWD disease subtype.

<table>
<thead>
<tr>
<th>VWD subtype</th>
<th>N</th>
<th>Response rate</th>
<th>Mean increase (fold)*</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>VWF:RCo</td>
<td>VWF:Ag</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [21]</td>
<td>15</td>
<td>N/A</td>
<td>N/A</td>
<td>3.6</td>
</tr>
<tr>
<td>de la Fuente et al. [22]</td>
<td>13</td>
<td>94%</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Mannucci et al. [23]</td>
<td>7</td>
<td>N/A</td>
<td>9.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Mannucci et al. [24]</td>
<td>15</td>
<td>N/A</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Federici et al. [17]</td>
<td>26</td>
<td>27%</td>
<td>3.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 1 Vincenza (rapid-clearing type)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannucci et al. [23]</td>
<td>6</td>
<td>N/A</td>
<td>9.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Rodeghiero et al. [25]</td>
<td>5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Castaman et al. [18]</td>
<td>22</td>
<td>N/A</td>
<td>11.4, 13.8‡</td>
<td>5.3, 8.5‡</td>
</tr>
<tr>
<td>Type 2A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de la Fuente et al. [22]</td>
<td>7</td>
<td>86%</td>
<td>6.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Revel-Vilk et al. [16]</td>
<td>5</td>
<td>40%†</td>
<td>4.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Federici et al. [17]</td>
<td>15</td>
<td>7%</td>
<td>2.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 2B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casonato et al. [26]</td>
<td>4</td>
<td>N/A</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>McKeown et al. [27]</td>
<td>3</td>
<td>N/A</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Castaman et al. [28]</td>
<td>33</td>
<td>N/A</td>
<td>Normalized in 18/33</td>
<td>Normalized in 33/33</td>
</tr>
<tr>
<td>Type 2M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federici et al. [17]</td>
<td>21</td>
<td>14%</td>
<td>3.3</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 2N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazurier et al. [29]</td>
<td>8</td>
<td>N/A</td>
<td>1.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Federici et al. [17]</td>
<td>4</td>
<td>75%</td>
<td>3.8</td>
<td>N/A</td>
</tr>
</tbody>
</table>


VWD, von Willebrand disease; VWF, von Willebrand factor; IV, intravenous; FVIII, factor VIII.

*Response defined as twofold increase and to at least 30 IU dL⁻¹ VWF:RCo and FVIII.

¶C1130F VWF mutation.

‡R1205H VWF mutation.

Data are given as mean fold increase in plasma factor compared to baseline after a single administration of DDAVP. Mean fold increases were calculated from original data, where possible, if not included in the manuscript.

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DDAVP in the treatment of bleeding

Small, single-institution series initially reported efficacy with the use of one to three doses of IV DDAVP for the treatment of typical bleeding events, including epistaxis, oral and soft tissue bleeding and rarely haemarthrosis [34,35]. One prospective clinical trial evaluated the treatment of bleeding with IV DDAVP in 18 patients with HA and three patients with VWD who had epistaxis, haemarthrosis, or intramuscular bleeding and other soft tissue bleeding. [22] Nine of 18 patients with haemophilia responded to DDAVP (one to three doses) without other infusion therapy, while the remaining patients had follow-up infusions of cryoprecipitate or FVIII concentrate. Six of eight patients who had an increase in baseline FVIII to ≥0.3 IU dL⁻¹ after DDAVP did not require additional FVIII therapy for the treatment of bleeding. All three VWD patients had a good response to IV DDAVP to control minor bleeding episodes [22].

Subsequently, two prospective studies were done to evaluate DDAVP use in the outpatient setting to allow for the rapid treatment of bleeding (Table 3). These studies evaluated the efficacy of IN and SC DDAVP used to treat spontaneous bleeding in over 500 outpatients with bleeding disorders (276 with VWD, 216 with HA, and 10 with other bleeding disorders) [36,37]. Both studies included children and adults, with a median age of 28 years in one study and a mean age of 23.9 years in the other. Haemostatic responses (efficacy rating of good or excellent) were achieved in 91–96% of all bleeding episodes, and no significant adverse events (AEs) were reported, suggesting that DDAVP is effective in home-based therapy.

One other prospective study was performed in a hospital setting for patients with VWD who were genetically typed to have rapid clearance of VWF after DDAVP administration; over a 6-year period, more than 80 patients were treated with SC DDAVP for bleeding with adequate efficacy [18]. Nevertheless, patients with rapid clearance variants of VWD may not benefit when prolonged elevations of FVIII:C or VWF are needed.

### DDAVP for surgical haemostasis

A number of both prospective and retrospective studies have described DDAVP use in the surgical setting (Table 4); IV DDAVP was used in nearly all reported surgical cases. While the majority of surgeries were adenotonsillar procedures or minor oral and dental surgeries, some reports of major surgery have been identified (Table 4) [1,18,22,35,38–45].

Early single-institution reports described the successful use of IV DDAVP in the management of patients with VWD or mild haemophilia A undergoing adenotonsillar procedures, with the adjunctive use of tranexamic acid or epsilon-aminocaproic acid. Vasomotor reaction (skin flushing) was the only appreciable AE reported in these series [17,25,28].

Subsequently, larger studies (including one prospective trial) of patients with VWD have reported data on more than 150 patients undergoing adenotonsillar procedures and have shown that DDAVP is generally effective and safe; most patients were children, although some adults were included as well. Treatment dosing regimens varied widely, ranging from a single dose (usually 0.3 μg kg⁻¹; although in some cases, 0.5 μg kg⁻¹ doses were used) to as many as five doses, and usually included adjunctive antifibrinolytic therapy (Table 4). Early postoperative bleeding was well controlled in patients who received two to four doses of DDAVP during the first week postoperatively; however, approximately 5–25% of patients experienced breakthrough bleeding 5–10 days postoperatively, suggesting that additional treatment may be needed prior to and at the time of eschar separation. Hyponatremia was more likely to occur with multiple DDAVP doses, and was minimized by careful attention to fluid restriction [38–41].

Other studies with larger patient populations reported good haemostasis in patients undergoing invasive dental procedures when one to three doses of DDAVP were used in conjunction with antifibrinolytic therapy.

### Table 3. Prospective studies of SC or IN DDAVP to treat bleeding in the homecare setting.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patient population</th>
<th>Mode of DDAVP delivery, dose (μg)</th>
<th>Bleeding frequency (haemorrhages/patient/year)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodeghiero et al. [36]</td>
<td>VWD (n = 100) 10–65 (median, 28)</td>
<td>SC: VWD: 1.27</td>
<td>Excellent: 64%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA (n = 69)</td>
<td>20 (&lt;70 kg)</td>
<td>Good: 27%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 (≥70 kg)</td>
<td>Ineffective: 9%</td>
<td></td>
</tr>
<tr>
<td>Leissinger et al. [37]</td>
<td>VWD (n = 176) 5.3–64.7 (mean, 23.9)</td>
<td>IN: –3.5</td>
<td>Excellent: 75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA (n = 147)</td>
<td>150 (&lt;50 kg)</td>
<td>Good: 21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (n = 10)</td>
<td>300 (&lt;50 kg)</td>
<td>Ineffective: 5%</td>
<td></td>
</tr>
</tbody>
</table>

VWD, von Willebrand disease; HA, haemophilia A; SC, subcutaneous; IN, intranasal.
Table 4. Clinical reports of DDAVP in surgical patients.

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Study type</th>
<th>N</th>
<th>Type of patients</th>
<th>Age (years)</th>
<th>DDAVP treatment and dose</th>
<th>Doses (n)</th>
<th>Days with doses*</th>
<th>Adjunctive therapies</th>
<th>Monitoring</th>
<th>Post-op bleeding</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenotonsillar</td>
<td>Prospective [38]</td>
<td>40</td>
<td>VWD Type 1</td>
<td>1.3–13 (5.2)</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>2–4</td>
<td>0-1, 2, 3 and/or 4</td>
<td>TA ×7 days</td>
<td>Daily sodium</td>
<td>Early: 2/40</td>
<td>Late: 0/40 Mild hyponatremia: 27/40 (67.5%) Severe hyponatremia: 2/40 (5%) Seizure: 1/40 (2.5%) Mild hyponatremia: 2/12 (16.7%) Severe hyponatremia: 3/12 (25%) Seizure: 1/69 (12.5%)</td>
</tr>
<tr>
<td>procedures</td>
<td>Retrospective [39]</td>
<td>12</td>
<td>VWD Type 1</td>
<td>2.5–9</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>Daily until eschar falls off</td>
<td>0-0</td>
<td>EACA or TA</td>
<td>Daily sodium</td>
<td>Early: 1/12</td>
<td>Late: 2/12</td>
</tr>
<tr>
<td></td>
<td>Retrospective [40]</td>
<td>69</td>
<td>VWD</td>
<td>1.5–17.3 (7.3)</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>1</td>
<td>0</td>
<td>Not reported</td>
<td>Sodium (in 53 patients)</td>
<td>Early: 7/69</td>
<td>Late: 9/69</td>
</tr>
<tr>
<td>Dental extractions</td>
<td>Prospective [22]</td>
<td>12</td>
<td>VWD (5)</td>
<td>8–60</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>1–7</td>
<td>0-0</td>
<td>TA ×5 days</td>
<td>None noted</td>
<td>Early: 0/41</td>
<td>Late: 7/41</td>
</tr>
<tr>
<td></td>
<td>Retrospective [1]</td>
<td>8</td>
<td>Mild HA (7)</td>
<td>&lt;18 (5.9)</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>3</td>
<td>0-0 and 5, 6, 7 or 8</td>
<td>EACA ×3-5 days</td>
<td>None noted</td>
<td>Early: 1/41</td>
<td>Late: 1/12</td>
</tr>
<tr>
<td></td>
<td>Retrospective [35]</td>
<td>25</td>
<td>VWD (9)</td>
<td>5-87</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>1</td>
<td>0</td>
<td>TA ×7 days</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>Retrospective [1]</td>
<td>1</td>
<td>Mild HA</td>
<td>1</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>2</td>
<td>0-1</td>
<td>TA None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Retrospective [43]</td>
<td>1</td>
<td>VWD</td>
<td>1</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>1</td>
<td>0</td>
<td>EACA None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Palate repair</td>
<td>Prospective [22]</td>
<td>1</td>
<td>HA</td>
<td>46</td>
<td>IV 0.5 µg kg⁻¹</td>
<td>1</td>
<td>0</td>
<td>None None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Retrospective [43]</td>
<td>1</td>
<td>VWD</td>
<td>1</td>
<td>IV 0.5 µg kg⁻¹</td>
<td>1</td>
<td>0</td>
<td>EACA None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>Retrospective [1]</td>
<td>1</td>
<td>VWD</td>
<td>1</td>
<td>IV 0.5 µg kg⁻¹</td>
<td>2</td>
<td>0-1</td>
<td>TA None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Retroperitoneal ganglina</td>
<td>Retrospective [35]</td>
<td>1</td>
<td>VWD</td>
<td>1</td>
<td>IV 0.3 µg kg⁻¹</td>
<td>5</td>
<td>0–2-4-6-8</td>
<td>TA None noted</td>
<td>None noted</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(continued)
therapy [1]. In a prospective study of 83 patients with a specific rapid VWF-clearance form of VWD, 20 patients underwent 28 dental extractions, with 24 receiving a single infusion of SC DDAVP followed by antifibrinolytic therapy for 5 days. No cases of immediate or delayed bleeding events were observed in these patients [18].

As previously noted, published experience on the use of DDAVP in major surgery is rare, with a few anecdotal case reports [1,35,43,44]. Due to DDAVP's limited usefulness over a prolonged duration, it is not expected to be effective in major surgeries.

DDAVP in the management of gynaecological and obstetrical bleeding

Menorrhagia

Menorrhagia, defined as the passage of > 80 mL of blood per month, is the most common complication that affects women with congenital bleeding disorders [46]. Several treatment modalities are available to control heavy menstrual bleeding, with selection determined by a patient's age and whether preservation of fertility is a concern. Hormonal therapies, including oral contraceptives, reduce menstrual blood flow and also raise FVIII:C and VWF levels [47]. DDAVP is an alternative approach for women who cannot take hormonal therapy or who are actively attempting to become pregnant. Two prospective studies in women with VWD or mild haemophilia A (i.e. haemophilia A carriers) have shown responses to DDAVP and antifibrinolytic therapy that were good or excellent in 86% and 92% of patients respectively (Table 5) [36,37]. Although no studies have investigated the relative efficacy of DDAVP and antifibrinolytic therapy, the combination may be more effective than either drug used individually.

Obstetric bleeding

The use of DDAVP during pregnancy is controversial because of the theoretical risk for premature labour, uterine contraction, and intrauterine growth retardation. Nevertheless, a systematic review of case reports and small case series reported good safety and efficacy with DDAVP [40]. A prospective study conducted at a third-trimester caesarean delivery centre reported a reduction in postpartum haemorrhage in 93% of patients treated with DDAVP [40]. DDAVP was well tolerated, and no adverse events were reported. However, DDAVP should not be used in women with a history of preterm delivery, as it may induce premature labour.

Table 4. (continued).

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Study type</th>
<th>N</th>
<th>Type of patients</th>
<th>Age (years)</th>
<th>DDAVP treatment and dose</th>
<th>Doses (n)</th>
<th>Days with doses*</th>
<th>Adjunctive therapies</th>
<th>Monitoring</th>
<th>Post-op bleeding</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral hernia repair</td>
<td>Retrospective [35]</td>
<td>1</td>
<td>HA Unk</td>
<td>0.3 µg kg⁻¹</td>
<td>5</td>
<td>0–0–1–2–3</td>
<td>TA None noted</td>
<td>None None noted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Retrospective [35]</td>
<td>1</td>
<td>HA Unk</td>
<td>0.3 µg kg⁻¹</td>
<td>3</td>
<td>0–1–2</td>
<td>TA None noted</td>
<td>None None noted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrococele</td>
<td>Retrospective [35]</td>
<td>1</td>
<td>VWD Unk</td>
<td>0.3 µg kg⁻¹</td>
<td>4</td>
<td>0–0–1–2</td>
<td>TA None noted</td>
<td>None None noted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meniscectomy</td>
<td>Retrospective [35]</td>
<td>1</td>
<td>HA Unk</td>
<td>0.3 µg kg⁻¹</td>
<td>3</td>
<td>0–1–2</td>
<td>TA None noted</td>
<td>None None noted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other minor surgeries</td>
<td>Prospective [22]</td>
<td>8</td>
<td>HA (6) VWD (2)</td>
<td>0.3 µg kg⁻¹</td>
<td>1–2</td>
<td>0–0–2</td>
<td>TA None noted</td>
<td>None None noted</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EACA, epsilon-aminocaproic acid; HA, haemophilia A; TA, tranexamic acid; Unk, unknown or not reported; VWD, von Willebrand disease; IV, intravenous; SC, subcutaneous.
*Numbers listed denote days on which doses were given; numbers listed twice indicate two doses were given on that day. 0 = day of surgery.
which adverse bleeding events were reported, there were four cases of postpartum haemorrhage and one case of SC haematoma. The underlying bleeding disorders in these women who developed bleeding complications despite treatment included two cases of Hermansky-Pudlak syndrome and a single case each of platelet storage pool disorder, EDS and VWD [48].

Other AEs associated with the use of DDAVP during pregnancy in the studies reviewed included one case of premature labour in the ninth month and one case of maternal seizure resulting from hyponatremia, both in patients with VWD. No neonatal complications or signs of intrauterine growth retardation were reported in the studies reviewed [48].

There have been no reports of teratogenic effects in foetuses exposed to DDAVP in the first trimester of pregnancy, and in vitro placental models show that DDAVP does not cross the placental barrier in detectable amounts [49,50]. DDAVP is released into breast milk in very small quantities, but there is negligible oral absorption, suggesting that maternal use during breastfeeding is safe [50,51]. Nonetheless, the manufacturer advises against use of DDAVP by nursing mothers.

**DDAVP safety**

Most AEs associated with DDAVP are mild and related to the vasomotor effects of the drug (e.g. headache, facial flushing, mild hypotension and tachycardia) [2,4]. The incidence of these effects is highly variable [37,38,40,41,52] and differs with the mode of administration, with more vasoactive AEs likely to occur with IV administration. In one study of IV DDAVP 0.3 μg kg⁻¹ in children with congenital bleeding disorders, mild cases of flushing and headache were reported in some patients [14]. However, infusing DDAVP over a 30- to 60-min period can attenuate these vasomotor effects. In a prospective study of the home use of SC DDAVP in 169 patients with VWD and mild or moderate haemophilia A, 30% reported mild flushing with or without headache, but these effects generally did not affect patient compliance [36]. Meanwhile, in a large prospective study of IN DDAVP in 278 patients with mild haemophilia A or mild or moderate type 1 VWD, or who were symptomatic carriers of haemophilia A, 172 (8%) doses were associated with AEs, with headache (3.6%) and flushing (3.2%) being most frequently reported, followed less frequently by dizziness (1.5%) and nausea (1.1%) [37].

Mild to severe hyponatremia and hyponatremia-related seizures are the most serious AEs linked to the use of DDAVP and are caused by its antidiuretic effect, which is 10 times greater with IV than with IN administration. Large case series suggest that hyponatremia in otherwise healthy adults is uncommon, and

<table>
<thead>
<tr>
<th>Patient population</th>
<th>DDAVP</th>
<th>Days/cycle treated</th>
<th>Efficacy</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 14</td>
<td>SC</td>
<td>Unknown</td>
<td>Excellent: 65%</td>
<td>Rodeghiero et al. [36]</td>
</tr>
<tr>
<td></td>
<td>20 μg (&lt;70 kg)</td>
<td>1-8 days</td>
<td>Good: 21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 μg (≥70 kg)</td>
<td>avg: 1.7 days</td>
<td>Ineffective: 14%</td>
<td></td>
</tr>
<tr>
<td>VWD and HA carriers</td>
<td>IN</td>
<td></td>
<td>Excellent + good: 92%</td>
<td>Leissinger et al. [37]</td>
</tr>
<tr>
<td>N = 90</td>
<td>150 μg (≤50 kg)</td>
<td>51% used 1 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 μg (≥50 kg)</td>
<td>25% used 2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14% used 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% used four or more days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Table 6. Important safety considerations with DDAVP. |
|-----------------|-----------------|-----------------|-----------------|
| Safety concerns  | Potential clinical effects | Potential severity of effects | Frequency | Comments |
| Vasomotor effects| Facial flushing, mild hypotension, and tachycardia | Mild | Common | Can usually be attenuated by slowing the infusion rate of DDAVP; it is recommended to give IV DDAVP over 30–60 min |
| Franchini et al. [2] | | | | |
| Antidiuretic effects | Hyponatremia, volume overload, and seizures | Serious | Less common | Particularly a problem in very young children, patients on diuretics, or patients who cannot control their fluid intake (those on IV fluids); more likely when patients receive multiple doses of DDAVP |
| Dunn et al. [52] | | | | |
| Das et al. [59] | | | | |
| Jiménez-Yuste et al. [38] | | | | |
| Smith et al. [55] | | | | |
| Thrombotic complications | Myocardial infarction and stroke | Life-threatening | Rare | DDAVP is generally avoided in patients with known atherosclerotic coronary artery disease, or poorly controlled hypertension |
| Bond et al. [57] | | | | |
| Byrne et al. [58] | | | | |
| Franchini et al. [60] | | | | |

IV, intravenous.
that incidence increases in young children with repetitive dosing or with overly aggressive fluid replacement during surgery [53–56]. Consequently, DDAVP is not recommended in children under 2 years of age, and fluid intake should be closely regulated in all patients [53,54]. In addition, DDAVP should be used with caution in persons with medical disorders associated with sodium abnormalities, such as cystic fibrosis, heart failure and renal disorders.

Because type 1 vasopressin receptors are minimally affected by DDAVP, the risk of uterine or gastrointestinal contractions or hypertension with treatment is low [4]. Rare instances of thrombotic complications (i.e. myocardial infarction, stroke) have been reported after DDAVP administration in elderly patients with cardiovascular and/or cerebrovascular risk factors, and the drug should be used cautiously in this patient population [57,58], as well as those with important risk factors for cardiovascular disease, such as poorly controlled hypertension. Table 6 provides a summary of potential safety concerns with DDAVP.

Conclusions

Clinical experience with DDAVP has greatly expanded over the past three decades. A recent study of practice patterns of a representative sampling of US haematologists caring for VWD patients showed that DDAVP was prescribed to treat over 80% of bleeding events, and used in over 85% of surgical procedures in patients with type 1 VWD, and in approximately 50% of bleeding events and 40% of surgical procedures in type 2 VWD [61]. This collective clinical experience with DDAVP is largely based on a growing literature of relatively small case series and a limited number of prospective non-randomized clinical trials.

When used in the treatment of bleeding, including menorrhagia in women, efficacy is good and significant AEs are rare, particularly when the number of doses is limited and there is attention to fluid restriction. Overall, given the potential benefits of rapid treatment of haemorrhages and the high level of safety and tolerability of DDAVP in older children and adults, the weight of evidence favours making DDAVP readily available for home use, with appropriate precautions regarding fluid restriction. Most patients are asked to limit their outpatient use to no more than two doses over a 24-h period, and to call their physician’s office if additional therapy is needed.

Surgery in patients with haemostatic disorders can be challenging and requires a deliberate and collaborative approach to achieve a successful outcome. Published studies of DDAVP for prevention of surgical bleeding have largely focused on ENT and dental surgery, with reports confirming good efficacy, especially when combined with antifibrinolytic therapy [42,50]. It is clear that a major risk period for bleeding occurs five or more days after the procedure at the time of eschar separation, and should serve as a reminder that additional therapy may be needed to prevent late postoperative bleeding. Although there are several case reports of its use in major surgery, DDAVP is not an appropriate treatment choice in most major surgical procedures requiring prolonged haemostasis because tachyphylaxis and concern over fluid retention precludes effective use over multiple days [24].

DDAVP is an important drug in the haemostatic armamentarium for patients with bleeding disorders. It has been successfully used in a wide variety of clinical settings in selected patients who have demonstrated responsiveness either by laboratory testing (in patients with VWD or haemophilia A) or clinical observation (in patients with other bleeding disorders). Compared to factor concentrates, DDAVP has the advantage of ease of administration (particularly with the IN formulation), convenience, low cost and avoidance of blood derivatives. In addition, responses can be readily monitored by following VWF or FVIII:C levels in patients with VWD and haemophilia A. DDAVP has also demonstrated a favourable safety profile, with most reported AEs being mild and related to its vasomotor effects.

While the collective clinical experience with DDAVP is largely based on anecdotal reports and small case series, the number of prospective and retrospective reports is accumulating. Our review of the published literature affirms the efficacy and safety of DDAVP for prevention and treatment of bleeding in selected patients with haemophilia A, VWD and other congenital bleeding disorders.

Disclosures

CL has acted as a paid consultant to Baxter, Bayer, Biogen Idec, CSL Behring, Kedrion, Novo Nordisk, and Pfizer, and has received research funding from Baxter, Bayer, CSL Behring and Novo Nordisk. MC has received honoraria/speaking fees from Baxter, Bayer, CSL Behring, Novo Nordisk, Octapharma, and Pfizer. MC has received research funds from Baxter, Bayer, Bio Sea, Novo Nordisk, and Pfizer. JCG has acted as a paid advisory board member to CS Behring, Octapharma, and Biogen Idec. JJ has received honoraria from Baxter Healthcare and Biogen Idec. JC has been on a grant review panel for Pfizer Hemophilia. TS has acted as a paid consultant for Kedron, Pfizer, and CSL Behring. She is a speaker for Grifols, Baxter, and Novo Nordisk. She has received grant funding from Baxter. Rush University Medical Center receives grant support on behalf of LV from Baxter Bioscience, Bayer Healthcare, Biogen, CSL Behring, GTC Biotherapeutics, Inspiration Bioscience, Novo Nordisk, and Pfizer, and Rush University Medical Center also receives payments on behalf of LV for his participation in advisory boards and as a consultant for Baxter Bioscience, Bayer Healthcare, Biogen, CSL Behring, GTC Biotherapeutics, Inspiration Bioscience, Novo Nordisk, and Pfizer.
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DDAVP IN THE MANAGEMENT OF BLEEDING DISORDERS


Desmopressin (DDAVP) in the Treatment of Bleeding Disorders: The First 20 Years

Pier Mannuccio Mannucci
Review Article

Desmopressin (DDAVP) in the Treatment of Bleeding Disorders:
The First 20 Years

By Pier Mannuccio Mannucci

In 1977 DESMOPRESSIN (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP), a derivative of the antidiuretic hormone, was used for the first time to treat patients with hemophilia A and von Willebrand disease (vWD), the most frequent congenital bleeding disorders. After the original clinical study performed in Italy, desmopressin was used in many other countries and the World Health Organization included it in the list of essential drugs. A drug that could raise the plasma levels of factor VIII and von Willebrand factor without the need of blood products was especially attractive in the late 1970s and early 1980s, when the human immunodeficiency virus began to be transmitted by infected coagulation factor concentrates to patients with congenital coagulation disorders.

The clinical indications for desmopressin quickly expanded beyond hemophilia and vWD. The compound was shown to be efficacious even in bleeding disorders not involving a deficiency or dysfunction of factor VIII or vWF, including congenital and acquired defects of platelet function and such frequent abnormalities of hemostasis as those associated with chronic kidney and liver diseases. Desmopressin has also been used prophylactically in patients undergoing surgical operations characterized by large blood loss and transfusion requirements.

Twenty years of clinical experience have now established more firmly the clinical indications of desmopressin. Some of these indications have been strengthened by the experience accumulated, others have not been supported by rigorous clinical trials or have been overcome by the advent of more efficacious treatments. This report reviews the spectrum of indications in bleeding disorders, in the attempt to establish which indications remain valid and which do not. Topics such as pharmacokinetics, pharmacodynamics, and side effects of desmopressin will not be dealt with because they are covered in previous reviews.

Historical Background

It was in 1772 when William Hewson noted that blood collected under conditions of stress clotted rapidly. Hewson’s observations, described in detail in An Inquiry into the Properties of the Blood, triggered a series of animal experiments performed by the physiologist Cannon and his associates at the beginning of this century. They showed that the enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma. In 1957, a possible mechanism for faster clotting after adrenaline was provided by Marciniak, who found a transient increase in coagulation factor VIII after injection in rabbits. Reports of raised factor VIII after adrenaline infusion in humans soon followed: the average increase was to about twice the starting level, with no measurable change in other clotting factors. In patients with mild hemophilia the magnitude of the factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals.

These findings stimulated further research, with the goal to identify a factor VIII–increasing agent that would be free of the side effects of adrenaline and could be administered to hemophilic patients as autologous replacement therapy. Vasopressin and insulin also induced an increase of factor VIII, but their side effects were not milder than those of adrenaline, making clinical use unrealistic. An important step forward was made with the observation that desmopressin, a synthetic analogue of vasopressin, increased factor VIII and vWF in healthy individuals. Unlike the natural antidiuretic hormone, desmopressin produced little or no vasoconstriction, no increase in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it was well tolerated when administered to humans.

A big step forward was taken when desmopressin was used in patients for the prevention and treatment of bleeding, first during dental extractions and then during major surgical procedures with mild hemophilia A or vWD. Surgery was performed without blood products, demonstrating that autologous factor VIII and vWF increased in patient plasma by desmopressin could effectively replace homologous factors contained in blood products. These clinical results were soon confirmed.
MECHANISMS OF ACTION OF DESMOPRESSIN

Despite 20 years of clinical use of desmopressin, mechanisms of action are still not completely understood. The increases in the plasma levels of factor VIII and vWF occur not only in deficient patients, but also in healthy individuals and in patients who already have high levels of these factors. Desmopressin shortens the prolonged activated partial thromboplastin time and the bleeding time. These effects probably result from the increases in factor VIII and vWF, which play a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall. Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin. Plasminogen activator generates plasmin in vivo, but most of the plasmin is quickly complexed to α2-antiplasmin and does not produce fibrinolysis in circulating blood. Accordingly, it is usually unnecessary to inhibit fibrinolysis when desmopressin is used for clinical purposes.

How do factor VIII and vWF increase in plasma? Because these factors increase rapidly and transiently, it is most likely that desmopressin causes them to be released from storage sites. The storage site(s) of factor VIII and the interaction between released factor VIII and concomitantly released vWF are not well established. The vascular endothelium is presumably the main source of vWF. This view is supported by the observation that in rats injections of desmopressin elicit biological responses that are clearly related to the activation of endothelial cells, like surface expression of P selectin and subsequent margination of leukocytes.

In normal individuals, desmopressin infusion produces important changes in the content and localization of vWF in vascular endothelial cells. There is a reduction in the amount of the protein and a change in its localization, which causes a tendency for the protein to move abluminally toward the cellular basement membrane. Notwithstanding these data focusing on the endothelial cell as the most likely source of vWF, addition of desmopressin to cultured endothelial cells in vitro does not release vWF. Even though cultured cells may not be identical to native cells and might have lost specific receptors during culture, these observations suggest an indirect action of desmopressin through a second messenger. In the search of such a second messenger, it was shown that release of vWF from endothelial cells occurred after the addition of desmopressin to monocytes. These data, and those implicating monocyte-derived platelet activating factor as the second messenger acting upon endothelial cells, need confirmation. Desmopressin acts on storage sites via its strong V2 agonist activity, since patients with nephrogenic diabetes insipidus, who are unresponsive to V2 agonists, do not have increased factor VIII and vWF levels after treatment with desmopressin. Anephric patients respond normally, indicating that the site of the V2-like receptors involved in the hemostatic properties of desmopressin is not in the kidney. Their location is currently unknown.

A puzzling, unresolved question is how desmopressin is efficacious in bleeding disorders other than hemophilia and vWD, in patients who have normal or even high levels of factor VIII and vWF. The favorable effects of the compound may be mediated by increased platelet adhesion to the vessel wall, due not only to the rise of plasma vWF but also to the abluminal secretion of the protein toward the subendothelium; by heightened coagulability, due to supranormal levels of factor VIII, a rate-accelerating factor in the process of fibrin formation; and by the fresh appearance in plasma of ultrasize vWF multimers. These are hemostatically very effective because they support to a higher degree platelet adhesion to the vascular subendothelium and induce platelet aggregation under conditions of high shear. Other putative mechanisms or mediators have been proposed to explain the hemostatic efficacy of desmopressin.

DESMPRESSIN IN THE MANAGEMENT OF CONGENITAL BLEEDING DISORDERS

In hemophilia and vWD, desmopressin is efficacious because it provides a form of autologous replacement therapy. Table 1 summarizes the routes of administration, the recommended dosages, and the pharmacokinetic properties of desmopressin-induced factor VIII and vWF.

The prototypes of patients who respond to desmopressin and avoid the use of coagulation factor concentrates are those with measurable levels of factor VIII and vWF, ie, patients with mild hemophilia A and type 1 vWD, whereas patients with unmeasurable levels do not respond at all. In mild hemophilia A the efficacy of desmopressin usually correlates with the postinfusion plasma levels of factor VIII. Accordingly, therapeutic indications are defined by the nature of the bleeding episode, the baseline factor VIII levels, and the levels that must be attained and maintained for hemostasis. Clinical failures of desmopressin can usually be explained by the attainment of factor VIII levels in plasma that are insufficient to control bleeding. For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmo-
pressin because the expected posttreatment levels of 30 to 50 U/dL are not high enough for hemostasis. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extractions.

Most patients with type 1 vWD respond to desmopressin with increases in factor VIII and vWF that are larger than those seen in hemophiliacs. In addition to factor VIII, in these patients a determinant of the clinical efficacy of the compound is its capacity to shorten or normalize the bleeding time. Although in type 1 vWD this effect is usually achieved in proportion to the levels of normally functioning vWF attained in plasma, the bleeding times of patients with type 3, characterized by complete deficiency of vWF, and of those with dysfunctional molecules are usually not shortened. There are, however, a few patients with type 2A vWD in whom desmopressin does shorten the bleeding time. The reasons for these different behaviors are not clear and a test dose is the only way to differentiate responders from nonresponders. In theory, the administration of desmopressin to patients with heightened interactions between platelet glycoprotein Ib and vWF (type 2B and platelet-type or “pseudo” vWD) might be potentially dangerous, because it is followed by platelet aggregation and, in most instances, by thrombocytopenia. Although there is some evidence that desmopressin is clinically efficacious in these patients (reviewed by Castaman and Rodeghiero), most hematologists would be reluctant to use it. Table 2 summarizes the indications for desmopressin in patients with different types of vWD.

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted. Some experimental data support this hypothesis because repeated infusions of desmopressin lower the amount of vWF contained in vascular endothelial cells. The average factor VIII responses obtained when desmopressin is repeated three to four times at 24-hour intervals are approximately 30% less than those obtained after the first dose. The clinical implications are that the efficacy of desmopressin may be limited when factor VIII levels must be maintained above the baseline levels for a prolonged period of time. In these situations, which occur relatively seldom in the clinical management of mild hemophilia and type 1 vWD, it may become necessary to use plasma-derived or recombinant factors, or to supplement desmopressin with them.

Subcutaneous and intranasal desmopressin are at least as efficacious as intravenous desmopressin and can be self-administered. Although intravenous desmopressin is recommended before surgery or for treating severe hemorrhages, because very consistent responses are required in these situations, subcutaneous desmopressin can be used at home to prevent or treat minor bleeding episodes and in women with vWD who have excessive bleeding at menstruation. Others prefer to use intranasal desmopressin as spray in these situations, even to handle major bleeding episodes and surgical operations.

Despite the fact that neither in vitro nor in vivo studies have clearly proved a direct stimulatory effect of desmopressin on platelets (reviewed by Wu et al), the drug shortens or normalizes the bleeding time of some patients with congenital defects of platelet function. Defects associated with normal dense granule stores benefit more from the compound.

Accordingly, there is usually a good response in patients with defects of the release reaction, with cyclooxygenase deficiency, and in those with isolated and unexplained prolongations of the bleeding time. Most patients with storage pool deficiency respond to desmopressin but a few do not, so a test dose is recommended to select responders. Whether the effect on a laboratory test such as the bleeding time corresponds to a hemostatic effect is not well established. On the other hand, the data obtained from a few well-conducted but nonrandomized studies would indicate that desmopressin can be a useful alternative to blood products during or after surgery or delivery, assuring satisfactory hemostasis.

To sum up, desmopressin is efficacious in mild hemophilia and type 1 vWD and usually permits the avoidance of concentrates, with significant reductions in costs. In the United States, for instance, an average dose of factor VIII concentrate (2,000 IU) costs between $800 and $2,000, depending on the source (plasma-derived or recombinant). An average dose of desmopressin (21 μg) is much cheaper ($100) and is even less expensive in Europe (the equivalent of $20 to $40). The benefits of desmopressin are not limited to cost savings. The compound may be needed to meet religious requests, such as the avoidance of blood products in Jehovah’s Witnesses. More importantly, it is likely to have spared many patients from infection with the human immunodeficiency virus type 1 (HIV). In Italy, where desmopressin was used earlier and more extensively than in other countries, the prevalence of HIV infection in patients with mild hemophilia (2.1%) is much lower than in patients with mild hemophilia B (13.5%). The latter is a suitable comparison group, because these patients need treatment at least as frequently as hemophilia A patients, but are unresponsive to desmopressin. Hence, they could only be treated with plasma concentrates during the critical years between 1977 (when desmopressin was first used clinically and the HIV outbreak started) and 1985 (when the outbreak was halted by the development of virus-inactivation methods and their application to plasma concentrates). Additional evidence of the HIV-sparing effect of desmopressin stems from the comparison of the prevalence of HIV infection in Italian patients with mild hemo-

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**Table 2. Indication for Desmopressin in Different Types of vWD**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Type 1, “platelet normal”</th>
<th>Type 2N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Type 1, “platelet low” and types 2A and 2B</td>
<td></td>
</tr>
<tr>
<td>Doubtful</td>
<td>Type 3 (severe)</td>
<td></td>
</tr>
</tbody>
</table>

“Established” indications are those in which desmopressin normalizes the bleeding time and factor VIII levels, and is clinically efficacious; “Possible” indications, those in which the effect on the bleeding time is absent or inconsistent, with little data on clinical efficacy; “Doubtful” indications, those in which desmopressin does not normalize factor VIII levels or the bleeding time, and is not clinically efficacious.
philic A to the corresponding patients from other countries where the compound was used later. In the United States, for instance, where in the period 1977-1985 mild hemophiliacs were mainly treated with plasma concentrates because desmopressin was not licensed until 1984, anti-HIV prevalence is 18.4%, nine times higher than in Italy.41

DESMOPRESSIN IN ACQUIRED AND DRUG-INDUCED BLEEDING DISORDERS

The hemostatic defect in uremia is characterized by a prolonged bleeding time, a laboratory abnormality that correlates strongly with the hemorrhagic symptoms of these patients, mainly epistaxis and bleeding from the gastrointestinal tract. Dialysis may improve the bleeding time and the bleeding tendency, but this is not always the case. In the search for pharmacological agents that could improve hemostasis in uremia, intravenous desmopressin was considered, despite the fact that factor VIII and vWF are normal in uremic patients.42 The postinfusion bleeding time became normal in about 75% of them, and returned to baseline values after approximately 8 hours.43 Well-conducted but noncontrolled clinical studies have shown that desmopressin can be used successfully to prevent bleeding before invasive procedures (biopsies and major surgery) and to stop spontaneous bleeding.42 Conjunctivae are a long-acting alternative to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days.43 The two products can be given together, exploiting the different timings of their maximal effects. Currently, most patients with chronic renal insufficiency are regularly treated with erythropoietin. This practice has led to the sustained improvement not only of anemia but also of the hemostatic defect,44 so that short-acting compounds such as desmopressin and conjugated estrogens are now less frequently needed.

The bleeding time is prolonged in some patients with liver cirrhosis. There is usually mild or moderate thrombocytopenia, but platelet counts do not correlate negatively with the bleeding time. Factor VIII and vWF are in the high normal range, or even higher, yet intravenous desmopressin shortens the bleeding time of cirrhotic patients.45,46 However, a controlled clinical trial has shown that desmopressin is not useful in the management of acute variceal bleeding in cirrhotic patients.47 Because this is the most frequent and serious hemorrhagic problem the overall clinical impact of desmopressin in liver cirrhosis is relatively small.

Desmopressin counteracts the effects on hemostasis measurements of some antithrombotic drugs. It shortens the prolonged bleeding time of individuals taking widely used antiplatelet agents such as aspirin and ticlopidine,46 the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin,48 and the bleeding time of rabbits treated with streptokinase49 or hirudin50 (without corresponding human data). It also counteracts the antihemostatic effects of dextran, with no apparent impairment of the antithrombotic properties.51

In summary, in chronic renal disease desmopressin remains indicated only for those patients with renal failure not treated or unresponsive to erythropoietin. Desmopressin is a possible treatment for patients with liver cirrhosis and prolonged bleeding time who need invasive diagnostic procedures such as liver biopsies. There is as yet little clinical evidence that desmopressin prevents or stops bleeding complications that develop in association with the use of antithrombotic agents. The compound may provide an opportunity to control drug-induced bleeding without stopping treatment and perhaps avoiding recurrence or progression of thrombosis.

DESMOPRESSIN AS A BLOOD-SAVING AGENT

The broadening indications of desmopressin, since the first use in hemophilia and vWD in 1977, led several investigators to evaluate whether the compound was beneficial during surgical operations in which blood loss is large and for which multiple blood transfusions are needed.

Open heart surgery with extracorporeal circulation is the epitome of operations that warrant the adoption of blood-saving measures. In addition to techniques such as presurgical removal of autologous blood for postsurgical retransfusion, returning all oxygenator and tubing contents to the patient, and autotransfusion of the mediastinal shed blood, prophylaxis with pharmacological agents might help reduce blood transfusion further. Since 1986, desmopressin has been evaluated for this purpose. In the first controlled randomized study carried out in patients undergoing complex cardiac operations associated with large blood losses, results were impressive.52 Given at the time of chest closure, desmopressin reduced dramatically perioperative and early (12 hours) postoperative blood loss and transfusion requirements by about one third.52 On the other hand, in two subsequent large studies of patients undergoing less complex operations with lesser blood loss, there were no significant differences between desmopressin- and placebo-treated patients in either total blood loss or transfusion requirements.53,54 Other studies, mainly in patients undergoing coronary artery bypass grafting and uncomplicated valve replacement, failed to find any benefit of desmopressin.55,56

The conflicting results of desmopressin in open heart surgery might be due to the fact that most studies were of small size and had insufficient statistical power to detect true differences in blood loss. A meta-analysis of 17 randomized, double-blind, placebo-controlled trials, which included 1,171 patients undergoing open heart surgery, has attempted to overcome this pitfall.57 Overall, desmopressin reduced postoperative blood loss by 9%, a value that is statistically significant but of little clinical impact. Although desmopressin had no blood-saving effect when the total blood loss in placebo-treated patients decreased in the lower and middle thirds of distribution (687 to 1,108 mL), the compound reduced blood losses by 34% when blood loss was larger.57 Therefore, desmopressin seems beneficial only in cardiac operations associated with large blood loss (>1 L). It is not easy to predict which patient will bleed more, but situations such as reoperation, presurgical use of antiplatelet agents, preexisting coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower preoperative plasma levels of factor VIII and vWF may also help to
acquired immunodeficiency syndrome (AIDS) could result have also been used, particularly after the recognition that mic acid and the broad-spectrum protease inhibitor aprotinin would be content with the outcome of his pioneer studies. It is of distinct interest that during his experiments at the moment. On the whole, more than 200 years establish the compound in these conditions (grade C recommendation based on level IV evidence). Currently, the widespread use of erythropoietin and the resulting sustained correction of the hemostatic defect make the use of desmopressin unnecessary in the majority of patients with chronic renal insufficiency. Antiﬁbrinolytic amino acids and aprotinin should be preferred to desmopressin in reducing blood loss and transfusion requirements during cardiac surgery with extracorporeal circulation (grade A recommendation based on level I evidence). The use of desmopressin in surgical operations other than cardiac surgery is not warranted at the moment. On the whole, more than 200 years of research have provided an agent that makes the blood clot faster, and William Hewson, who so ingeniously inquired into the properties of blood in the 18th century, perhaps would be content with the outcome of his pioneer studies.

identify patients most at risk of bleeding. However, the overlap of values is so large that it is not possible to use these measurements to select patients with the most to gain from the use of desmopressin.

Desmopressin is not the only blood-saving agent that can be used in cardiac surgery. The synthetic antiﬁbrinolytic amino acids epsilon-aminocaproic acid (EACA) and tranexamic acid and the broad-spectrum protease inhibitor aprotinin have also been used, particularly after the recognition that acquired immunodeﬁciency syndrome (AIDS) could result from blood transfusions contaminated with HIV. A few direct comparison studies and a meta-analysis have shown that the order of efﬁcacy of these hemostatic agents (greatest to least) is aprotinin, tranexamic acid, EACA, and desmopressin. On the other hand, the order of drug cost is also the same. Cost-effectiveness analysis is necessary to help the clinicians in making a choice that currently would be directed to aprotinin, but with formidable costs.

The efﬁcacy of desmopressin has also been evaluated in noncardiac surgical operations characterized by large blood loss. When administered to hemostatically normal children before spinal fusion for idiopathic scoliosis, desmopressin reduced their average operative blood loss by about one third, but these favorable results were not conﬁrmed in a subsequent study. Desmopressin did not reduce blood loss or transfusion requirement after total hip or knee arthroplasty. Preoperative desmopressin failed to reduce blood loss in patients undergoing debridement and grafting of burn wounds, a procedure in which extreme blood loss is a frequent occurrence.

In summary, the efﬁcacy of desmopressin as a blood-saving agent in cardiac and noncardiac surgical operations appears doubtful at the moment.

### THERAPEUTIC GUIDELINES

The main therapeutic guidelines for desmopressin are summarized in Table 3 and are graded upon the criteria proposed by the Agency for Health Care Policy and Research Publications of the US Department of Health and Human Services. Twenty years after the ﬁrst clinical application, the compound is still the treatment of choice for patients with mild hemophilia A and type 1 vWD (grade B recommendation). The evidence of its efﬁcacy as autologous replacement of the deﬁcient factors is so clear that no randomized controlled clinical trial was ever necessary (level III evidence). In patients with congenital defects of platelet function, with the hemostatic abnormalities associated with chronic liver disease and with those induced by the therapeutic use of antplatelet and anticoagulant agents, desmopressin has been used successfully to prevent or stop bleeding. However, there is still no well-designed clinical trial that truly shows efﬁcacy of the compound in these conditions (grade C recommendation based on level IV evidence). Currently, the widespread use of erythropoietin and the resulting sustained correction of the hemostatic defect make the use of desmopressin unnecessary in the majority of patients with chronic renal insufficiency. Antiﬁbrinolytic amino acids and aprotinin should be preferred to desmopressin in reducing blood loss and transfusion requirements during cardiac surgery with extracorporeal circulation (grade A recommendation based on level I evidence). The use of desmopressin in surgical operations other than cardiac surgery is not warranted at the moment. On the whole, more than 200 years of research have provided an agent that makes the blood clot faster, and William Hewson, who so ingeniously inquired into the properties of blood in the 18th century, perhaps would be content with the outcome of his pioneer studies.

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DESMOPRESSIN (DDAVP) IN THE TREATMENT OF BLEEDING DISORDERS

Revised edition

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Introduction

In 1977 desmopressin (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP), a synthetic derivative of the antidiuretic hormone, was used for the first time to treat patients with hemophilia A and von Willebrand disease (VWD), the most frequent congenital bleeding disorders [1]. After the original clinical study performed in Italy, desmopressin was used in many other countries and the World Health Organization included it in the list of essential drugs. A drug that could raise plasma levels of factor VIII and von Willebrand factor (VWF) without the need of blood products was especially attractive in the late 1970s and early 1980s, a time when the human immunodeficiency virus (HIV) began to be transmitted by infected coagulation factor concentrates to patients with congenital coagulation disorders.

The potential clinical indications for desmopressin quickly expanded beyond hemophilia and VWD. The compound was claimed to be efficacious in bleeding disorders not involving a deficiency or dysfunction of factor VIII or VWF, including congenital and acquired defects of platelet function and such frequent abnormalities of hemostasis as those associated with chronic kidney and liver disease. Desmopressin has also been used prophylactically in patients undergoing surgical procedures characterized by significant blood loss and transfusion requirements, especially cardiac and orthopedic surgery.

Thirty-five years of clinical experience have now established more firmly the clinical indications of desmopressin. Some of these indications have been strengthened by the experience accumulated, while others have not been supported by rigorous clinical trials or have been overcome by the advent of more efficacious treatments. This report reviews the spectrum of indications in bleeding disorders, in an attempt to establish which indications remain valid and which do not. The pharmacokinetics, pharmacodynamics, and side effects of desmopressin have been dealt with in previous reviews [2-4].

Historical background

In 1772, William Hewson noticed that blood collected under conditions of stress clotted rapidly [5]. Hewson’s observations, described in detail in An Inquiry into the Properties of the Blood, triggered a series of animal experiments performed by the physiologist Cannon and his associates at the beginning of the 20th century. They showed that the enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma [6, 7]. In 1957, a mechanism for faster clotting after adrenaline was provided by Marciniak [8], who found a transient increase in coagulation factor VIII after injection in rabbits. Reports of raised factor VIII after adrenaline infusion in humans soon followed: the average increase was to about twice the starting level, with no measurable change in other coagulation factors [9]. In patients with mild hemophilia, the magnitude of factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals [9, 10]. These findings stimulated further research, with the goal of identifying a factor VIII-increasing agent free of the side effects of adrenaline that could be administered to people with hemophilia as autologous replacement therapy.

Vasopressin and insulin were shown to induce an increase of factor VIII [11], but their side effects were not milder than those of adrenaline, making clinical use unrealistic. An important step forward was made with the observation that desmopressin, a synthetic analogue of vasopressin, increased factor VIII and VWF in healthy individuals [12, 13]. Unlike the natural antidiuretic hormone, desmopressin produces little or no vasoconstriction, no increase
in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it is well tolerated when administered to humans [12,13].

A big step forward was made when desmopressin was used for the prevention and treatment of bleeding, first during dental extractions and then during major surgical procedures in patients with mild hemophilia A or VWD [1]. Surgery was performed without blood products, demonstrating that autologous factor VIII and VWF increased in patient plasma and that desmopressin could effectively replace homologous factors contained in blood products [1]. These clinical results were soon confirmed [14-16].

Mechanism of action

The increase in plasma levels of factor VIII and VWF occur not only in deficient patients, but also in healthy individuals and in patients who already have high levels of these factors. Desmopressin shortens the prolonged activated partial thromboplastin time and the bleeding time [17]. These effects probably result from the rise in factor VIII and VWF, which plays a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no dramatic effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall [18,19]. Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin [12,13]. Plasminogen activator generates plasmin in vivo, but most of the plasmin is quickly complexed to $\alpha_2$ -antiplasmin, so that it does not produce fibrin(ogen)olysis in circulating blood [20]. Accordingly, it is usually unnecessary to inhibit fibrinolysis when desmopressin is used for clinical purposes.

How do factor VIII and VWF increase in plasma? Because the increase is rapid and transient, it is most likely that desmopressin causes these factors to be released from storage sites. The vascular endothelium is presumably the main source of VWF. This view is supported by the observation that, in rats, injections of desmopressin elicit biological responses that are clearly related to the activation of endothelial cells, such as surface expression of P-selectin and subsequent margination of leukocytes [21]. In normal individuals, desmopressin infusion produces important changes in the content and localization of VWF in vascular endothelial cells [22]. There is a reduction in the amount of the protein and a change in its localization, which causes a tendency for the protein to move abluminally toward the cellular basement membrane [22].

Notwithstanding these data focusing on the endothelial cell as the most likely source of VWF, addition of desmopressin to cultured endothelial cells in vitro does not release VWF [23]. This apparent paradox was solved by the demonstration that the lack of direct effect of desmopressin on human vascular endothelial cells (HUVEC) is attributable to the fact that these cells do not express the V2 receptor (V2R) [24]. When desmopressin was added to cultured HUVEC transfected to express V2R or to lung microvascular endothelial cells (which naturally express V2R), the compound did elicit a release of VWF, which was mediated by an increase in intracellular cAMP [24].

The interactions between released factor VIII and concomitantly released VWF and tPA are not well established. The observation that patients with VWD type 3 treated with desmopressin not only fail to release VWF (which is not synthesized in these patients), but also factor VIII and tPA (which are normally synthesized), supports the hypothesis that these effects are regulated by a single mechanism defective in type 3 VWD [25].

The site of cellular storage and release of factor VIII is less well established than that of VWF [26]. Desmopressin did elicit the expected VWF rise but no factor VIII rise in dogs with hemophilia A after hepatocyte-driven neonatal gene therapy [27]. This observation suggests that the increase of factor VIII induced by desmopressin in normal dogs and perhaps in humans is due to its release from cells other than the hepatocyte, perhaps endothelial cells where factor VIII is co-localized and complexed with VWF [27].

That the cellular co-localization of factor VIII and VWF is required for the plasma rise in factor VIII after desmopressin is also demonstrated by the observation that, following liver transplantation, patients with hemophilia A infused with desmopressin showed the expected VWF rise but no change in plasma factor VIII [28]. Because factor VIII is synthesized only in the transplanted liver, this observation supports the views that co-localization of factor VIII and VWF in extrahepatic cells is necessary for in vivo release of factor VIII after desmopressin [28].
Desmopressin (DDAVP) in the Treatment of Bleeding Disorders

Desmopressin in the management of congenital bleeding disorders

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The patients who respond to desmopressin and avoid the use of coagulation factor concentrates are those with measurable levels of factor VIII and VWF, i.e. patients with mild hemophilia A and type 1 VWD, [14-16], whereas patients with unmeasurable levels do not respond at all [17]. In mild hemophilia A, the efficacy of desmopressin usually correlates with the post-infusion plasma levels of factor VIII [14-16]. Accordingly, therapeutic indications are defined by the nature of the bleeding episode, the baseline factor VIII levels, and the levels that must be attained and maintained for hemostasis.

Clinical failures of desmopressin can usually be explained by the attainment of factor VIII levels in plasma that are insufficient to control bleeding. For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmopressin, because the expected post-treatment levels of 30 to 50 U/dL are not high enough to secure hemostasis. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extraction.

Most patients with type 1 VWD, who have a functionally normal VWF but reduced plasma levels, respond to desmopressin with plasma increases in factor VIII and VWF that are usually larger than those seen in people with hemophilia [29,30]. Hence, desmopressin should be the first choice for treatment of these patients. There is, however, some variability in response to desmopressin between patients with type 1 VWD [31-33]. The reasons for these different behaviours are not clear and a test dose is the only way to distinguish good responders from poor or non-responders. The defects of patients with type 3 VWD and of those with dysfunctional molecules (type 2 VWD) are usually not corrected by desmopressin, with some exceptions [34,35].

General guidelines for the use of desmopressin or plasma product in the different subtypes of VWD are given in Table 2, which shows the schedule of desmopressin administration and blood sampling recommended to evaluate the degree of laboratory response to a test dose. On the basis of the results obtained, one can predict whether the attained factor levels and the duration of their persistence in plasma are sufficient to successfully manage a given clinical situation.

### TABLE 1. Recommended dosages of desmopressin and factor VIII/VWF responses in patients with hemophilia and VWD

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Route</th>
<th>Mean factor increase over baseline (range)</th>
<th>Time to peak levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 μg/kg</td>
<td>Intravenous and subcutaneous</td>
<td>2-4 times (1.5-20 times)</td>
<td>30-60 min after intravenous injection</td>
</tr>
<tr>
<td>300 μg/kg</td>
<td>Intranasal</td>
<td></td>
<td>90-120 min after subcutaneous injection and intranasal application</td>
</tr>
<tr>
<td>2-4 times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-8 hours</td>
<td></td>
<td></td>
<td></td>
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Desmopressin in the management of congenital bleeding disorders

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted [29]. Some experimental data support this hypothesis, because repeated infusions of desmopressin lower the amount of VWF contained in vascular endothelial cells [22]. The average factor VIII responses obtained if desmopressin is repeated at 24-hour intervals are approximately 30% less than those obtained after the first dose [29]. The clinical implications are that the efficacy of desmopressin may be limited when factor VIII levels must be maintained above the baseline levels for a prolonged period of time. In these situations, which occur relatively seldom in the clinical management of mild hemophilia and type 1 VWD, it may become necessary to use plasma-derived or recombinant factors, or to supplement desmopressin with them.
Subcutaneous and intranasal desmopressin are at least as efficacious as intravenous desmopressin and can be self-administered. Although intravenous desmopressin is recommended before surgery or for treating severe hemorrhages, because very consistent responses are required in these situations, subcutaneous desmopressin can be used at home to prevent or treat minor bleeding episodes and in women with VWD who have excessive bleeding at menstruation [36]. Others prefer to use intranasal desmopressin in these situations, even to handle major bleeding episodes and surgical operations [37].

Despite the fact that neither in vitro nor in vivo studies have clearly proved a direct stimulatory effect of desmopressin on platelets (reviewed by Wun et al) [38], the drug shortens or normalizes the bleeding time of some patients with congenital defects of platelet function [39,40]. Defects associated with normal dense granule stores benefit more from the compound [40]. Accordingly, there is usually a good response in patients with defects of the release reaction, with cyclooxygenase deficiency, and in those with isolated and unexplained prolongations of the bleeding time.

Most patients with storage pool deficiency respond to desmopressin but a few do not [40], so a test dose is recommended to select responders. Whether the effect on a laboratory test such as the bleeding time corresponds to a hemostatic effect is not well-established. On the other hand, the data obtained from a few well-conducted but non-randomized studies would indicate that desmopressin can be a useful alternative to blood products during or after surgery or delivery, assuring satisfactory hemostasis [39,40].

To sum up, desmopressin is efficacious in mild hemophilia and type 1 VWD and usually permits the avoidance of concentrates, with significant reductions in costs. In the United States, for instance, an average dose of factor VIII concentrate (2,000 IU) costs between US$1,000 and $2,000. An average dose of desmopressin (21 μg) is much cheaper (US$100) and is even less expensive in Europe (the equivalent of US$20-$40).

The benefits of desmopressin are not limited to cost savings. The compound may be needed to meet religious requests, such as the avoidance of blood products in Jehovah’s witnesses. More importantly, it is likely to have spared many patients from infection of the type 1 human immunodeficiency virus (HIV). In Italy, where desmopressin was used earlier and more extensively than in other countries, the prevalence of HIV infection in patients with mild hemophilia (2.1%) was much lower than in patients with mild hemophilia B (13.5%) [41]. The latter is a suitable comparison group, because these patients need treatment as frequently as hemophilia A patients, but are unresponsive to desmopressin. Hence, they could only be treated with plasma concentrates during the critical years between 1977 (when desmopressin was first used clinically and the HIV outbreak started) and 1985-1987 (when the outbreak was halted by the development of virus-inactivation methods and their application to plasma concentrates). Additional evidence of the HIV-sparing effect of desmopressin stems from the comparison of the prevalence of HIV infection in Italian patients with mild hemophilia A to the corresponding patients from other countries where the compound was used later. In the United States, for instance, where in the period 1977-1985 people with mild hemophilia were mainly treated with plasma concentrates because desmopressin was not yet licensed, anti-HIV prevalence is 18.4%, nine times higher than in Italy [41].

**Desmopressin in acquired and drug-induced bleeding disorders**

The hemostatic defect in uremia is characterized by a prolonged bleeding time, a laboratory abnormality that correlates with the hemorrhagic symptoms of these patients, mainly epistaxis and bleeding from the gastrointestinal tract. Dialysis may improve the bleeding time and the bleeding tendency, but this is not always the case. In the search for pharmacological agents that could improve hemostasis in uremia, desmopressin was considered, despite the fact that factor VIII and VWF are normal or even high in uremic patients [42]. The post-infusion bleeding time became normal in about 75%, and returned to baseline values after approximately 8 hours [42].

Well-conducted but non-controlled clinical studies have shown that desmopressin can be used successfully to prevent bleeding before invasive procedures (biopsies and major surgery) and to stop spontaneous bleeding [42]. Conjugated estrogens are a long-acting alternative
to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days [43]. The two products can be given together, exploiting the different timings of their maximal effects. Currently, most patients with chronic renal insufficiency are regularly treated with erythropoietin. This practice has led to the sustained improvement not only of anemia but also of the hemostatic defect [44], so that short-acting compounds such as desmopressin and conjugated estrogens are unusually needed.

The bleeding time is prolonged in some patients with liver cirrhosis. There is usually mild or moderate thrombocytopenia, but platelet counts do not correlate negatively with the bleeding time. Factor VIII and VWF are in the high-normal range, or even higher, yet intravenous desmopressin shortens the bleeding time of cirrhotic patients [45,46]. However, a controlled clinical trial has shown that desmopressin is not useful in the management of acute variceal bleeding in cirrhotic patients [47]. Because this is the most frequent and serious hemorrhagic problem, the overall clinical impact of desmopressin in liver cirrhosis is relatively small.

Desmopressin counteracts the effects of some antithrombotic drugs on hemostasis measurements. It shortens the prolonged bleeding time of individuals taking antiplatelet agents, the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin [48], and the bleeding time of rabbits treated with streptokinase [49] or hirudin [50] (without corresponding human data). It also counteracts the antihemostatic effects of dextran, with no apparent impairment of the antithrombotic properties [51].

In summary, in chronic renal disease desmopressin remains indicated only for those patients with renal failure not treated or unresponsive to erythropoietin. Desmopressin is a possible treatment for patients with liver cirrhosis and prolonged bleeding time who need invasive diagnostic procedures such as liver biopsies. Notwithstanding the fact that there is only preliminary evidence that desmopressin prevents or stops bleeding complications that develop in association with the use of antithrombotic agents, the compound may provide an opportunity to control drug-induced bleeding without stopping treatment and perhaps avoiding recurrence or progression of thrombosis.

Desmopressin as a blood-saving agent

The broadening indications of desmopressin led several investigators to evaluate whether or not the compound was beneficial during surgical operations in which blood loss is great and for which multiple blood transfusions are needed.

Open-heart surgery with extracorporeal circulation is the epitome of operations that warrant the adoption of blood-saving measures. In addition to techniques such as pre-surgical removal of autologous blood for post-surgical retransfusion, returning all oxygenator and tubing contents to the patient, and autotransfusion of the mediastinal shed blood, prophylaxis with pharmacological agents might help reduce blood transfusion further.

Since 1986 desmopressin has been evaluated for this purpose. In the first controlled randomized study carried out in patients undergoing complex cardiac operations associated with large blood losses, results were impressive [52]. On the other hand, in subsequent large studies of patients undergoing less complex operations with lesser blood loss, there were no significant differences between desmopressin- and placebo-treated patients in either total blood loss or transfusion requirements [53,54]. Other studies, mainly in patients undergoing coronary artery bypass grafting and uncomplicated valve replacement, failed to find any benefit of desmopressin [55,56].

The conflicting results of desmopressin in open-heart surgery might be due to the fact that most studies were of small size and had insufficient statistical power to detect true differences in blood loss. A meta-analysis of 17 randomized, double-blind, placebo-controlled trials, which included 1,171 patients undergoing open-heart surgery, has attempted to overcome this pitfall [57]. Overall, desmopressin reduced post-operative blood loss by 9%, a value that is statistically significant but of little clinical impact. Although desmopressin had no blood-saving effect when the total blood loss in placebo-treated patients decreased in the lower- and middle-thirds of distribution (687 to 1,108 ml), the compound reduced blood losses by 34% when blood loss was larger [57]. The modest results obtained with desmopressin were substantially confirmed in a more recent meta-analysis of 38 randomized, placebo-controlled trials on 2,488 undergoing various surgical procedures (mainly cardiac surgery) [58].
Therefore, desmopressin seems beneficial only in operations associated with large blood loss (>1 l). It is not easy to predict which patient will bleed more, but situations such as re-operation, pre-surgical use of antiplatelet agents, pre-existing coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower pre-operative plasma levels of factor VIII and VWF may also help to identify patients most at risk of bleeding [52,53]. However, the overlap of values is so large that it is not possible to use these measurements to select patients with the most to gain from the use of desmopressin.

Desmopressin is not the only blood-saving agent that can be used in cardiac surgery. The synthetic antifibrinolytic amino acids aminocaproic acid (EACA) and tranexamic acid, and the broad-spectrum protease inhibitor aprotinin have also been used, particularly after the recognition that acquired immunodeficiency syndrome (AIDS) could result from blood transfusions contaminated with HIV. A few direct comparison studies [59,60] and a meta-analysis [61] have shown that the order of efficacy of these hemostatic agents (greatest to least) is aprotinin, tranexamic acid, EACA, and desmopressin [61]. The order of drug cost is also the same. However, aprotinin has been withdrawn from use in cardiac surgery because it was shown to be associated with an increased death rate associated with cardiovascular complications [62].

TABLE 3. Indications for desmopressin in the treatment of bleeding disorders

<table>
<thead>
<tr>
<th>Grading of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
</tr>
<tr>
<td>Mild hemophilia A</td>
<td>B</td>
</tr>
<tr>
<td>VWD (see Table 2)</td>
<td>B</td>
</tr>
<tr>
<td>Possible</td>
<td></td>
</tr>
<tr>
<td>Congenital defects of platelet function</td>
<td>C</td>
</tr>
<tr>
<td>Uremia</td>
<td>C</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>C</td>
</tr>
<tr>
<td>Drug-induced bleeding (heparin, hirudin, antiplatelet agents, dextran, streptokinase)</td>
<td>C</td>
</tr>
<tr>
<td>Doubtful</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>A</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>A</td>
</tr>
</tbody>
</table>

In summary, the efficacy of desmopressin as a blood-saving agent in cardiac and noncardiac surgical operations appears doubtful at the moment.

**Therapeutic guidelines**

The main therapeutic guidelines for desmopressin are summarized in Table 3. It is the treatment of choice for patients with mild hemophilia A and type 1 VWD (grade B recommendation). The evidence of its efficacy as autologous replacement of the deficient factors is so clear that no randomized controlled clinical trial was ever necessary (level III evidence).

In patients with congenital defects of platelet function, with the hemostatic abnormalities associated with chronic liver disease, and with those induced by the therapeutic use of antiplatelet and anticoagulant agents, desmopressin has been used successfully to prevent or stop bleeding. However, there is still no well-designed clinical trial that truly shows efficacy of the compound in these conditions (grade C recommendation based on level IV evidence).
Currently, the widespread use of erythropoietin and the resulting sustained correction of the hemostatic defect make the use of desmopressin unnecessary in the majority of patients with chronic renal insufficiency. Antifibrinolytic amino acids should be preferred to desmopressin in reducing blood loss and transfusion requirements during cardiac surgery with extracorporeal circulation (grade A recommendation based on level I evidence).

The use of desmopressin in surgical operations other than cardiac surgery is not warranted at the moment. On the whole, more than 200 years of research have provided an agent that makes the blood clot faster, and William Hewson, who so ingeniously inquired into the properties of blood in the 18th century, perhaps would be content with the outcome of his pioneer studies.

References


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Desmopressin (DDAVP) in the Treatment of Bleeding Disorders


DESMOPRESSIN (DDAVP) IN THE TREATMENT OF BLEEDING DISORDERS

Revised edition

Pier Mannuccio Mannucci
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center
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DESMPRESSIN (DDAVP) IN THE TREATMENT OF BLEEDING DISORDERS
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Introduction

In 1977 desmopressin (1-deamino-8-D-arginine vasopressin, abbreviated DDAVP), a synthetic derivative of the antidiuretic hormone, was used for the first time to treat patients with hemophilia A and von Willebrand disease (VWD), the most frequent congenital bleeding disorders [1]. After the original clinical study performed in Italy, desmopressin was used in many other countries and the World Health Organization included it in the list of essential drugs. A drug that could raise plasma levels of factor VIII and von Willebrand factor (VWF) without the need of blood products was especially attractive in the late 1970s and early 1980s, a time when the human immunodeficiency virus (HIV) began to be transmitted by infected coagulation factor concentrates to patients with congenital coagulation disorders.

The potential clinical indications for desmopressin quickly expanded beyond hemophilia and VWD. The compound was claimed to be efficacious in bleeding disorders not involving a deficiency or dysfunction of factor VIII or VWF, including congenital and acquired defects of platelet function and such frequent abnormalities of hemostasis as those associated with chronic kidney and liver disease. Desmopressin has also been used prophylactically in patients undergoing surgical procedures characterized by significant blood loss and transfusion requirements, especially cardiac and orthopedic surgery.

Thirty-five years of clinical experience have now established more firmly the clinical indications of desmopressin. Some of these indications have been strengthened by the experience accumulated, while others have not been supported by rigorous clinical trials or have been overcome by the advent of more efficacious treatments. This report reviews the spectrum of indications in bleeding disorders, in an attempt to establish which indications remain valid and which do not. The pharmacokinetics, pharmacodynamics, and side effects of desmopressin have been dealt with in previous reviews [2-4].

Historical background

In 1772, William Hewson noticed that blood collected under conditions of stress clotted rapidly [5]. Hewson’s observations, described in detail in An Inquiry into the Properties of the Blood, triggered a series of animal experiments performed by the physiologist Cannon and his associates at the beginning of the 20th century. They showed that the enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma [6,7]. In 1957, a mechanism for faster clotting after adrenaline was provided by Marciniak [8], who found a transient increase in coagulation factor VIII after injection in rabbits. Reports of raised factor VIII after adrenaline infusion in humans soon followed: the average increase was to about twice the starting level, with no measurable change in other coagulation factors [9]. In patients with mild hemophilia, the magnitude of factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals [9,10]. These findings stimulated further research, with the goal of identifying a factor VIII-increasing agent free of the side effects of adrenaline that could be administered to people with hemophilia as autologous replacement therapy.

Vasopressin and insulin were shown to induce an increase of factor VIII [11], but their side effects were not milder than those of adrenaline, making clinical use unrealistic. An important step forward was made with the observation that desmopressin, a synthetic analogue of vasopressin, increased factor VIII and VWF in healthy individuals [12,13]. Unlike the natural antidiuretic hormone, desmopressin produces little or no vasoconstriction, no increase
in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it is well tolerated when administered to humans [12,13].

A big step forward was made when desmopressin was used for the prevention and treatment of bleeding, first during dental extractions and then during major surgical procedures in patients with mild hemophilia A or VWD [1]. Surgery was performed without blood products, demonstrating that autologous factor VIII and VWF increased in patient plasma and that desmopressin could effectively replace homologous factors contained in blood products [1]. These clinical results were soon confirmed [14-16].

Mechanism of action

The increase in plasma levels of factor VIII and VWF occur not only in deficient patients, but also in healthy individuals and in patients who already have high levels of these factors. Desmopressin shortens the prolonged activated partial thromboplastin time and the bleeding time [17]. These effects probably result from the rise in factor VIII and VWF, which plays a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no dramatic effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall [18,19]. Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin [12,13]. Plasminogen activator generates plasmin in vivo, but most of the plasmin is quickly complexed to $\alpha_2$-antiplasmin, so that it does not produce fibrin(ogen)olysis in circulating blood [20]. Accordingly, it is usually unnecessary to inhibit fibrinolysis when desmopressin is used for clinical purposes.

How do factor VIII and VWF increase in plasma? Because the increase is rapid and transient, it is most likely that desmopressin causes these factors to be released from storage sites. The vascular endothelium is presumably the main source of VWF. This view is supported by the observation that, in rats, injections of desmopressin elicit biological responses that are clearly related to the activation of endothelial cells, such as surface expression of P-selectin and subsequent margination of leukocytes [21]. In normal individuals, desmopressin infusion produces important changes in the content and localization of VWF in vascular endothelial cells [22]. There is a reduction in the amount of the protein and a change in its localization, which causes a tendency for the protein to move abluminally toward the cellular basement membrane [22].

Notwithstanding these data focusing on the endothelial cell as the most likely source of VWF, addition of desmopressin to cultured endothelial cells in vitro does not release VWF [23]. This apparent paradox was solved by the demonstration that the lack of direct effect of desmopressin on human vascular endothelial cells (HUVEC) is attributable to the fact that these cells do not express the V2 receptor (V2R) [24]. When desmopressin was added to cultured HUVEC transfected to express V2R or to lung microvascular endothelial cells (which naturally express V2R), the compound did elicit a release of VWF, which was mediated by an increase in intracellular cAMP [24].

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In hemophilia and VWD, desmopressin is efficacious because it provides a form of autologous replacement therapy. Table 1 summarizes the routes of administration, the recommended dosages, and the pharmacokinetic properties of desmopressin-induced factor VIII and VWF.

<table>
<thead>
<tr>
<th>Single dose</th>
<th>Intravenous and subcutaneous: 0.3 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean factor increase over baseline</td>
<td>2-4 times (range: 1.5-20 times)</td>
</tr>
<tr>
<td>Time to peak levels</td>
<td>30-60 min after intravenous injection</td>
</tr>
<tr>
<td></td>
<td>90-120 min after subcutaneous injection and intranasal application</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>5-8 hours for factor VIII</td>
</tr>
<tr>
<td></td>
<td>8-10 hours for VWF</td>
</tr>
</tbody>
</table>

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Clinical failures of desmopressin can usually be explained by the attainment of factor VIII levels in plasma that are insufficient to control bleeding. For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmopressin, because the expected post-treatment levels of 30 to 50 U/dL are not high enough to secure hemostasis. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extraction.

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**TABLE 2. Indication for desmopressin in different types of VWD**

<table>
<thead>
<tr>
<th>Established</th>
<th>Type 1, “platelet normal”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2N</td>
<td></td>
</tr>
</tbody>
</table>

| Possible    | Type 1, “platelet low” and types 2A and 2B |

| Doubtful    | Type 3 (severe) |

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted [29]. Some experimental data support this hypothesis, because repeated infusions of desmopressin lower the amount of VWF contained in vascular endothelial cells [22]. The average factor VIII responses obtained if desmopressin is repeated at 24-hour intervals are approximately 30% less than those obtained after the first dose [29]. The clinical implications are that the efficacy of desmopressin may be limited when factor VIII levels must be maintained above the baseline levels for a prolonged period of time. In these situations, which occur relatively seldom in the clinical management of mild hemophilia and type 1 VWD, it may become necessary to use plasma-derived or recombinant factors, or to supplement desmopressin with them.
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Most patients with storage pool deficiency respond to desmopressin but a few do not [40], so a test dose is recommended to select responders. Whether the effect on a laboratory test such as the bleeding time corresponds to a hemostatic effect is not well-established. On the other hand, the data obtained from a few well-conducted but non-randomized studies would indicate that desmopressin can be a useful alternative to blood products during or after surgery or delivery, assuring satisfactory hemostasis [39,40].

To sum up, desmopressin is efficacious in mild hemophilia and type 1 VWD and usually permits the avoidance of concentrates, with significant reductions in costs. In the United States, for instance, an average dose of factor VIII concentrate (2,000 IU) costs between US$1,000 and $2,000. An average dose of desmopressin (21 μg) is much cheaper (US$100) and is even less expensive in Europe (the equivalent of US$20-$40).

The benefits of desmopressin are not limited to cost savings. The compound may be needed to meet religious requests, such as the avoidance of blood products in Jehovah’s witnesses. More importantly, it is likely to have spared many patients from infection of the type 1 human immunodeficiency virus (HIV). In Italy, where desmopressin was used earlier and more extensively than in other countries, the prevalence of HIV infection in patients with mild hemophilia (2.1%) was much lower than in patients with mild hemophilia B (13.5%) [41]. The latter is a suitable comparison group, because these patients need treatment as frequently as hemophilia A patients, but are unresponsive to desmopressin. Hence, they could only be treated with plasma concentrates during the critical years between 1977 (when desmopressin was first used clinically and the HIV outbreak started) and 1985-1987 (when the outbreak was halted by the development of virus-inactivation methods and their application to plasma concentrates). Additional evidence of the HIV-sparing effect of desmopressin stems from the comparison of the prevalence of HIV infection in Italian patients with mild hemophilia A to the corresponding patients from other countries where the compound was used later. In the United States, for instance, where in the period 1977-1985 people with mild hemophilia were mainly treated with plasma concentrates because desmopressin was not yet licensed, anti-HIV prevalence is 18.4%, nine times higher than in Italy [41].

Desmopressin in acquired and drug-induced bleeding disorders

The hemostatic defect in uremia is characterized by a prolonged bleeding time, a laboratory abnormality that correlates with the hemorrhagic symptoms of these patients, mainly epistaxis and bleeding from the gastrointestinal tract. Dialysis may improve the bleeding time and the bleeding tendency, but this is not always the case. In the search for pharmacological agents that could improve hemostasis in uremia, desmopressin was considered, despite the fact that factor VIII and VWF are normal or even high in uremic patients [42]. The post-infusion bleeding time became normal in about 75%, and returned to baseline values after approximately 8 hours [42].

Well-conducted but non-controlled clinical studies have shown that desmopressin can be used successfully to prevent bleeding before invasive procedures (biopsies and major surgery) and to stop spontaneous bleeding [42]. Conjugated estrogens are a long-acting alternative
to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days [43]. The two products can be given together, exploiting the different timings of their maximal effects. Currently, most patients with chronic renal insufficiency are regularly treated with erythropoietin. This practice has led to the sustained improvement not only of anemia but also of the hemostatic defect [44], so that short-acting compounds such as desmopressin and conjugated estrogens are unusually needed.

The bleeding time is prolonged in some patients with liver cirrhosis. There is usually mild or moderate thrombocytopenia, but platelet counts do not correlate negatively with the bleeding time. Factor VIII and VWF are in the high-normal range, or even higher, yet intravenous desmopressin shortens the bleeding time of cirrhotic patients [45,46]. However, a controlled clinical trial has shown that desmopressin is not useful in the management of acute variceal bleeding in cirrhotic patients [47]. Because this is the most frequent and serious hemorrhagic problem, the overall clinical impact of desmopressin in liver cirrhosis is relatively small.

Desmopressin counteracts the effects of some antithrombotic drugs on hemostasis measurements. It shortens the prolonged bleeding time of individuals taking antplatelet agents, the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin [48], and the bleeding time of rabbits treated with streptokinase [49] or hirudin [50] (without corresponding human data). It also counteracts the antihemostatic effects of dextran, with no apparent impairment of the antithrombotic properties [51].

In summary, in chronic renal disease desmopressin remains indicated only for those patients with renal failure not treated or unresponsive to erythropoietin. Desmopressin is a possible treatment for patients with liver cirrhosis and prolonged bleeding time who need invasive diagnostic procedures such as liver biopsies. Notwithstanding the fact that there is only preliminary evidence that desmopressin prevents or stops bleeding complications that develop in association with the use of antithrombotic agents, the compound may provide an opportunity to control drug-induced bleeding without stopping treatment and perhaps avoiding recurrence or progression of thrombosis.

### Desmopressin as a blood-saving agent

The broadening indications of desmopressin led several investigators to evaluate whether or not the compound was beneficial during surgical operations in which blood loss is great and for which multiple blood transfusions are needed.

Open-heart surgery with extracorporeal circulation is the epitome of operations that warrant the adoption of blood-saving measures. In addition to techniques such as pre-surgical removal of autologous blood for post-surgical retransfusion, returning all oxygenator and tubing contents to the patient, and autotransfusion of the mediastinal shed blood, prophylaxis with pharmacological agents might help reduce blood transfusion further.

Since 1986 desmopressin has been evaluated for this purpose. In the first controlled randomized study carried out in patients undergoing complex cardiac operations associated with large blood losses, results were impressive [52]. On the other hand, in subsequent large studies of patients undergoing less complex operations with lesser blood loss, there were no significant differences between desmopressin- and placebo-treated patients in either total blood loss or transfusion requirements [53,54]. Other studies, mainly in patients undergoing coronary artery bypass grafting and uncomplicated valve replacement, failed to find any benefit of desmopressin [55,56].

The conflicting results of desmopressin in open-heart surgery might be due to the fact that most studies were of small size and had insufficient statistical power to detect true differences in blood loss. A meta-analysis of 17 randomized, double-blind, placebo-controlled trials, which included 1,171 patients undergoing open-heart surgery, has attempted to overcome this pitfall [57]. Overall, desmopressin reduced post-operative blood loss by 9%, a value that is statistically significant but of little clinical impact. Although desmopressin had no blood-saving effect when the total blood loss in placebo-treated patients decreased in the lower- and middle-thirds of distribution (687 to 1,108 ml), the compound reduced blood losses by 34% when blood loss was larger [57]. The modest results obtained with desmopressin were substantially confirmed in a more recent meta-analysis of 38 randomized, placebo-controlled trials on 2,488 undergoing various surgical procedures (mainly cardiac surgery) [58].
Therefore, desmopressin seems beneficial only in operations associated with large blood loss (>1 l). It is not easy to predict which patient will bleed more, but situations such as re-operation, pre-surgical use of antiplatelet agents, pre-existing coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower pre-operative plasma levels of factor VIII and VWF may also help to identify patients most at risk of bleeding [52,53]. However, the overlap of values is so large that it is not possible to use these measurements to select patients with the most to gain from the use of desmopressin.

Desmopressin is not the only blood-saving agent that can be used in cardiac surgery. The synthetic antifibrinolytic amino acids aminocaproic acid (EACA) and tranexamic acid, and the broad-spectrum protease inhibitor aprotinin have also been used, particularly after the recognition that acquired immunodeficiency syndrome (AIDS) could result from blood transfusions contaminated with HIV. A few direct comparison studies [59,60] and a meta-analysis [61] have shown that the order of efficacy of these hemostatic agents (greatest to least) is aprotinin, tranexamic acid, EACA, and desmopressin [61]. The order of drug cost is also the same. However, aprotinin has been withdrawn from use in cardiac surgery because it was shown to be associated with an increased death rate associated with cardiovascular complications [62].

The efficacy of desmopressin has also been evaluated in noncardiac surgical operations characterized by large blood loss. When administered to hemostatically normal children before spinal fusion for idiopathic scoliosis, desmopressin reduced their average operative blood loss by about one third [63], but these favorable results were not confirmed in a subsequent study [64]. Desmopressin did not reduce blood loss or transfusion requirement after total hip or knee arthroplasty [65].

In summary, the efficacy of desmopressin as a blood-saving agent in cardiac and noncardiac surgical operations appears doubtful at the moment.

**Therapeutic guidelines**

The main therapeutic guidelines for desmopressin are summarized in Table 3. It is the treatment of choice for patients with mild hemophilia A and type 1 VWD (grade B recommendation). The evidence of its efficacy as autologous replacement of the deficient factors is so clear that no randomized controlled clinical trial was ever necessary (level III evidence).

In patients with congenital defects of platelet function, with the hemostatic abnormalities associated with chronic liver disease, and with those induced by the therapeutic use of antiplatelet and anticoagulant agents, desmopressin has been used successfully to prevent or stop bleeding. However, there is still no well-designed clinical trial that truly shows efficacy of the compound in these conditions (grade C recommendation based on level IV evidence).

---

**TABLE 3. Indications for desmopressin in the treatment of bleeding disorders**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Grading of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hemophilia A</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>VWD (see Table 2)</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital defects of platelet function</td>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>Uremia</td>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>Drug-induced bleeding (heparin, hirudin, antiplatelet agents, dextran, streptokinase)</td>
<td>C</td>
<td>IV</td>
</tr>
<tr>
<td>Doubtful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>A</td>
<td>I</td>
</tr>
</tbody>
</table>
Currently, the widespread use of erythropoietin and the resulting sustained correction of the hemostatic defect make the use of desmopressin unnecessary in the majority of patients with chronic renal insufficiency. Antifibrinolytic amino acids should be preferred to desmopressin in reducing blood loss and transfusion requirements during cardiac surgery with extracorporeal circulation (grade A recommendation based on level I evidence).

The use of desmopressin in surgical operations other than cardiac surgery is not warranted at the moment. On the whole, more than 200 years of research have provided an agent that makes the blood clot faster, and William Hewson, who so ingeniously inquired into the properties of blood in the 18th century, perhaps would be content with the outcome of his pioneer studies.

References


47. de Franchis F, Arcidiacono PG, Carpinelli PG, Andreoni B, Cestari L, Brunati S, Zambelli A, Battaglia G, Mannucci PM. Randomized controlled trial of...


Apply separately to the plate as 10 mm bands 5 μL of each solution. Develop immediately over a path of 15 cm using a mixture of 3 volumes of water R, 36 volumes of methanol R and 130 volumes of methylene chloride R. Dry the plate in a current of warm air, spray with a mixture of 5 volumes of sulfuric acid R and 95 volumes of alcohol R and heat at 140 °C for 15 min. Examine in daylight. In the chromatogram obtained with test solution (a), any band, apart from the principal band, is not more intense than the band in the chromatogram obtained with reference solution (b) (2.5 per cent) and at most two such bands are more intense than the band in the chromatogram obtained with reference solution (c) (1.0 per cent).

**Loss on drying** (2.2.32). Not more than 0.5 per cent, determined on 0.500 g. by drying in vacuo at 105 °C.

**Sulfated ash** (2.4.14). Not more than 0.1 per cent, determined on the residue obtained in the test for loss on drying.

**ASSAY**
Dissolve 50.0 mg in alcohol R and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with alcohol R. Prepare a reference solution in the same manner, using 50.0 mg of deslanoside CRS (undried). To 5.0 mL of each solution add 3.0 mL of alkaline sodium picrate solution R and allow to stand protected from bright light in a water-bath at 20 ± 1 °C for 40 min. Measure the absorbance (2.2.25) of each solution at the maximum, at 484 nm, using as the compensation liquid a mixture of 3.0 mL of alkaline sodium picrate solution R and 5.0 mL of alcohol R prepared at the same time. Calculate the content of C16H22O12S2 from the absorbances measured and the concentrations of the solutions.

**STORAGE**
Store in an airtight, glass container, protected from light, at a temperature below 10 °C.

### TESTS

**Specific optical rotation** (2.2.7): −72 to −82 (anhydrous and acetic acid-free substance).

Dissolve 10.0 mg in a 1 per cent V/V solution of glacial acetic acid R and dilute to 5.0 mL with the same acid.

**Related substances.** Liquid chromatography (2.2.29): use the normalisation procedure.

**Test solution.** Dissolve 1.0 mg of the substance to be examined in 2.0 mL of water R.

**Resolution solution.** Dissolve the contents of a vial of oxytocin/desmopressin validation mixture CRS in 500 μL of water R.

**Column:**
- size: l = 0.12 m, O = 4.0 mm;
- stationary phase: octadecylsilyl silica gel for chromatography R (5 μm).

**Mobile phase:**
- mobile phase A: 0.067 M phosphate buffer solution pH 7.0 R; filter and degas;
- mobile phase B: acetonitrile for chromatography R; mobile phase A (50:50 V/V); filter and degas.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (per cent V/V)</th>
<th>Mobile phase B (per cent V/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>4 - 18</td>
<td>76 → 58</td>
<td>24 → 42</td>
</tr>
<tr>
<td>18 - 35</td>
<td>58 → 48</td>
<td>42 → 52</td>
</tr>
<tr>
<td>35 - 40</td>
<td>48 → 76</td>
<td>52 → 24</td>
</tr>
<tr>
<td>40 - 50</td>
<td>76</td>
<td>24</td>
</tr>
</tbody>
</table>

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 50 μL.

**Retention time:** desmopressin = about 16 min; oxytocin = about 17 min.

**System suitability:** resolution solution:
- resolution: minimum 1.5 between the peaks due to desmopressin and oxytocin.

**Limits:**
- unspecified impurities: for each impurity, maximum 0.5 per cent;
- total: maximum 1.5 per cent;
- disregard limit: 0.05 per cent.

**Acetic acid** (2.5.34): 3.0 per cent to 8.0 per cent.

Test solution. Dissolve 20.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

**Water** (2.5.32): maximum 6.0 per cent, determined on 20.0 mg.

**Bacterial endotoxins** (2.6.14): less than 500 IU/mg; if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.
Desogestrel

### ASSAY
Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

**Reference solution.** Dissolve the contents of a vial of desmopressin CRS in water R to obtain a concentration of 0.5 mg/mL.

**Mobile phase:** mobile phase B, mobile phase A (40:60 V/V).

**Flow rate:** 2.0 mL/min.

**Retention time:** desmopressin ≈ 5 min.

Calculate the content of desmopressin (C₄₆H₆₄N₁₄O₁₂S₂) from the declared content of C₄₆H₆₄N₁₄O₁₂S₂ in desmopressin CRS.

### STORAGE
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

### LABELLING
The label states:
- the mass of peptide per container;
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

### IMPURITIES
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use): A, B, C, D, E, F, G.

**Mobile phase:** mobile phase B (specification)

**Flow rate:** 1.0 mL/min.

**Detection:** spectrophotometer at 205 nm.

**Injection:** 15 μL of the test solution and reference solutions (a), (b) and (c).

**Run time:** 2.5 times the retention time of desogestrel.

**Identification of impurities:** use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

**Relative retention** with reference to desogestrel (retention time = about 22 min): impurity E = about 0.2; impurity D = about 0.25; impurity B = about 0.7; impurity A = about 0.95; impurity C = about 1.05.

**System suitability:** reference solution (a):
- peak-to-valley ratio: minimum 2.0, where \( H_p \) = height above the baseline of the peak due to impurity C and \( H_v \) = height above the baseline of the lowest point of the curve separating this peak from the peak due to desogestrel.

**Limits:**
- correction factors: for the calculation of content, multiply the peak area of the following impurities by the corresponding correction factor: impurity A = 1.8, impurity D = 1.5;
- impurities A, B, C: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- impurity D: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

**DEFINITION**
13-Ethyl-11-methylidene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol.

**CHARACTERS**
Appearance: white or almost white, crystalline powder.

**Solubility:** practically insoluble in water, very soluble in methanol, freely soluble in anhydrous ethanol and in methylene chloride.

### IDENTIFICATION
A. Infrared absorption spectrophotometry (2.2.24).

**Comparison:** desogestrel CRS.

**B. Specific optical rotation** (see Tests).

### TESTS
**Specific optical rotation** (2.2.7): +53 to +57 (dried substance).

**Test solution.** Dissolve 20.0 mg of the substance to be examined in 25 mL of acetonitrile R1 and dilute to 50.0 mL with water R.

**Reference solution (a).** Dissolve 4 mg of desogestrel for system suitability CRS (containing impurities A, B, C and D) in 5 mL of acetonitrile R1 and dilute to 10.0 mL with water R.

**Reference solution (b).** Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

**Reference solution (c).** Dilute 1.0 mL of reference solution (b) to 10.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

**Reference solution (d).** Dissolve 20.0 mg of desogestrel CRS in 25 mL of acetonitrile R1 and dilute to 50.0 mL with water R.

**Column:**
- size: l = 0.25 m, Ø = 4.6 mm,
- stationary phase: sterically protected octadecylsilyl silica gel for chromatography R (5 μm),
- temperature: 50 °C.

**Mobile phase:** water R, acetonitrile R1 (27:73 V/V).

**Flow rate:** 1.0 mL/min.

**Detection:** spectrophotometer at 205 nm.

**Injection:** 15 μL of the test solution and reference solutions (a), (b) and (c).

**Run time:** 2.5 times the retention time of desogestrel.

**Identification of impurities:** use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

**Relative retention** with reference to desogestrel (retention time = about 22 min): impurity E = about 0.2; impurity D = about 0.25; impurity B = about 0.7; impurity A = about 0.95; impurity C = about 1.05.

**System suitability:** reference solution (a):
- peak-to-valley ratio: minimum 2.0, where \( H_p \) = height above the baseline of the peak due to impurity C and \( H_v \) = height above the baseline of the lowest point of the curve separating this peak from the peak due to desogestrel.

**Limits:**
- correction factors: for the calculation of content, multiply the peak area of the following impurities by the corresponding correction factor: impurity A = 1.8, impurity D = 1.5;
- impurities A, B, C: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
- impurity D: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);