Review of Anticoagulant Drugs in Paediatric Thromboembolic Disease

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Summary
1. Intent of Review
To review the indications for anticoagulant therapies in children.
To review the epidemiology of thromboembolic events in children.
To review the literature and collate the evidence regarding dosing, administration and monitoring of anticoagulant therapies in childhood.
To review the safety of anticoagulant therapies and supervision required
To give recommendations for the inclusion of anticoagulants on the WHO Essential Medicines List

2. Review of indications for antithrombotic therapy in children
Anticoagulant therapies are given for the prevention or treatment of venous and/or arterial thrombosis. The process of ‘development haemostasis’, whereby the proteins involved in coagulation change quantitatively and qualitatively with age across childhood, essentially protects children against thrombosis(1-5). For this reason, insults such as immobilization are unlikely to trigger the development of thrombotic diseases in children. Even if inherited genetic predisposition is present in children, they are unlikely to develop a thrombosis until adulthood(2). As a result, the epidemiology of thromboembolic disease differs between children and adults, with the majority of thrombotic events diagnosed in children being iatrogenic (2, 6-8).

However, this finding likely reflects the state of this disease in developed countries, where advanced surgical and medical approaches are used to treat and palliate life-threatening conditions. There is very little evidence reporting the prevalence of thromboembolic diseases in developing countries. A Medline search using key words, “thrombosis or stroke”, ‘developing countries’ and limited to humans, the English language and all children identified 20 articles: of these, only 1 actually included episodes of thromboembolic disease in children(9). As such, recommendations for the management of thromboembolic disease in childhood are very much limited to tertiary paediatric populations in developed countries.

**Venous Thromboembolism (VTE)**

The risk factor most frequently identified as the leading contributor of VTE in childhood is the placement of central venous access devices(6, 8). Other conditions associated with the development of VTE in childhood include malignancy, vascular malformations, trauma or surgery (8, 10-12). The reported incidence of VTE in children ranges from 0.07/10,000 Canadian children in the community to 5.3-8.0/10,000 children admitted to tertiary hospitals(8, 10). Children who develop spontaneous VTE are likely to be adolescents with some form of inherited or acquired thrombophilia (8, 10). The rate of inherited and acquired thrombophilia conditions varies depending upon the ethnic origin of a population. For example, the prevalence of thrombophilia in childhood is significantly higher in mainland Europe than in Australian and North American studies investigating VTE in childhood (8, 10, 13).

Demonstrating the significant underlying health problems associated with VTE in childhood, the all-cause mortality associated with a concomitant diagnosis of VTE in one study population was 8.4%, with 15% of children who survived to discharge having significant VTE-related morbidity at follow-up (8).
Arterial Thromboembolism (ATE)

Similar to VTE, ATE is unlikely to occur in healthy children. No registry data reporting the incidence of ATE in healthy children is available. For hospitalized children however, ATE occurs with a similar prevalence to VTE. A 2-year prospective registry of ATE in an Australian tertiary paediatric centre identified an incidence of 8.5/10,000 hospital admissions (7). Children presenting with ATE usually have multiple pre-disposing factors present, including placement of intra-arterial devices, vascular malformations, surgery and congenital heart disease (7). One subset of patients presenting with ATE are children with Arterial Ischaemic Stroke AIS). In children, AIS may develop secondary to congenital heart disease due to right-to-left shunts, or seemingly unprovoked(6, 14, 15).

Arterial thromboembolism in childhood is associated with significant morbidity and mortality. The only prospective registry of ATE in childhood determined a direct ATE-related mortality rate of 9%, with 49% of children who survived to discharge being diagnosed with long-term physiological deficits associated with their ATE(7).

3. Anticoagulant Drugs

Unfractionated heparin (UFH)

a. Mechanism of action and pharmacology

Unfractionated heparin is a heterogeneous glycosaminoglycan with a molecular weight ranging from 3000 to 30,000 kD (16-21). Whilst UFH used for clinical purposes was initially isolated from the livers of pigs and dogs, the majority of commercial UFH preparations currently available are isolated from porcine intestinal mucosa or bovine lung (19). The majority of UFH binding occurs due to electrostatic attraction, however the binding of UFH to antithrombin (AT) is highly specific and dependent upon a unique pentasaccharide sequence located on ‘high affinity’ UFH molecules (22, 23). ‘High affinity’ UFH fractions with a molecular weight greater than 5000Da are able to inhibit thrombin and factor Xa, whilst UFH fractions with a molecular weight of less than 5000Da preferentially promote inhibition of factor Xa only(20, 24, 25). In the presence of UFH, AT’s inhibition of coagulation serine proteases increases approximately 1000-fold(26). In addition, UFH increases the intravascular release of tissue factor pathway inhibitor (TFPI) (27-36). Three to ten minutes following the injection of UFH, TFPI release from the vascular endothelium increases in a dose and concentration dependent fashion(34). Between one third and one half of the thrombin inhibition achieved following the administration of UFH in vivo is attributable to TFPI (30).

b. Dosing and administration of UFH

Few randomized controlled trials of UFH dosing, route of administration or duration of therapy have been conducted in paediatric populations. The majority of evidence available is based upon a handful of cohort studies in children at risk of thrombosis or who have been diagnosed with a thrombosis.

Original research studies reporting evidence related to the dosing, administration and/or monitoring of UFH in children was identified from a Medline search (1950-2009). The key word was ‘Heparin’, and the search was limited to ‘Administration
and Dosing’, ‘English Language’, ‘Humans’ and ‘All Child’ (0-18years). 281 papers identified. 20 papers provided details regarding unfractionated heparin dosing and/or monitoring in children. Studies reporting the use of UFH for the maintenance of vascular catheters were excluded. Table 1 summarises the studies identified.

The American College of Chest Physicians produces evidence-based guidelines for the management of antithrombotic therapy every 3 years. Within this volume of work there is a chapter dedicated to Antithrombotic therapy in children. For each recommendation regarding dosing and administration of UFH, the grade of evidence associated with that recommendation is listed. Due to the lack of well-designed randomized controlled trials generating evidence regarding optimal dosing, administration and monitoring, the bulk of these recommendations has a Grade 2 level of evidence(6).
<table>
<thead>
<tr>
<th>Author/date</th>
<th>Study design</th>
<th>Study population (incl. N)</th>
<th>Age Distribution</th>
<th>Dosing recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ekert 1973(37)</strong></td>
<td>Cohort study</td>
<td>Haemolytic Uraemic Syndrome (n=9); Disseminated Intravascular Coagulopathy (N= 8); Purpura fulminans (n=1)</td>
<td>15 days to 8.5 yrs</td>
<td>- UFH administered from day of diagnosis</td>
<td>- UFH effect measured using aPTT.</td>
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<td></td>
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<td>- Loading doses of 100-400units/kg</td>
<td>- aPTT demonstrated significant intra- and inter-individual variation, both within disease groups and between groups.</td>
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<td>- Infusion doses to maintain aPTT 1.5-2.5 times normal.</td>
<td>- 1 cerebral haemorrhage and 1 major bleeding from renal biopsy site – both fatal.</td>
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<td>- Duration of Rx: HUS (7days); DIC (8 days); PF (23 days)</td>
<td>4 ‘minor’ bleeding events (no a priori definitions were given).</td>
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<tr>
<td><strong>Freed, Keane and Rosenthal 1974(38)</strong></td>
<td>Double-blinded RCT</td>
<td>n=161 Children and young adults undergoing cardiac angiography.</td>
<td>1-34 years (median 11yrs) All patients &gt; 10kg</td>
<td>- 100-150unit/kg UFH bolus versus placebo.</td>
<td>No recommendation</td>
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<td>- In children &lt; 10yrs of age, 100units/kg UFH significantly reduced the rate of cool, pulseless extremities following cardiac angiography compared to placebo (p=0.003).</td>
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<tr>
<td><strong>McDonald 1982(39)</strong></td>
<td>Prospective cohort study</td>
<td>N=15 Infants (term and preterm) with documented venous or arterial thromboembolism</td>
<td>25 weeks gestation, day 1 to 28 month old term baby.</td>
<td>- Bolus of 50-100units/kg followed by infusion rate of 10-20units/kg/hr</td>
<td>UFH concentration measured using anti-Xa assay</td>
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<td>- UFH effect measured using Laidlaw Whole Blood Clotting Time</td>
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<td>- r² of anti-Xa and WBCT was 0.47</td>
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<td>- Good clinical outcome for 14 of 15 infants. One child required amputation of digits</td>
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<td>- Used mathematical equations, not pharmacokinetic methods, to determine UFH clearance in infants. This suggested infants had increased clearance compared to adults.</td>
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<tr>
<td><strong>von Kries, Stannigel and Gobel 1985(40)</strong></td>
<td>Cohort study of &quot;heparin activated antithrombin (AT) concentrate” newborns</td>
<td>N=10 Newborn infants with Disseminated Intravascular Coagulopathy and life-threatening illness who had poor UFH response or low AT levels.</td>
<td>Gestational ages ranged from 30-40 weeks. No details re age at time of UFH.</td>
<td>- UFH and AT was mixed and continuously infused in 5% glucose</td>
<td>UFH effect measured using thrombin clotting time.</td>
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<td>- Doses ranged from 20-40 units/kg/day of AT and 50-500units/kg/day UFH.</td>
<td>- Study did not evaluate the method of monitoring.</td>
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<td>- Authors concluded that 40units/kg/day of AT and 200units/kg/day UFH achieved the best thrombin clotting time for treatment benefit</td>
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<tr>
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<tr>
<td>Netz et al 1987(41)</td>
<td>Prospective</td>
<td>N=120 Infants and children requiring cardiac angiography</td>
<td>No age ranges given.</td>
<td>UFH dose = 100units/kg Patients were divided into:</td>
<td>- UFH effect measured by ACT</td>
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<td></td>
<td>cohort study</td>
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<td>- infants with cyanotic heart disease (25)</td>
<td>- ACT demonstrated UFH response differed between infants and children, regardless of heart disease</td>
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<td>- infants with acyanotic heart disease (25)</td>
<td>- ACT demonstrated UFH response differed between cyanotic and acyanotic heart disease, regardless of age.</td>
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<td>- children with cyanotic heart disease (25)</td>
<td>- No multivariate analyses were conducted to determine the independent impact of age</td>
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<td>- children with acyanotic heart disease (45)</td>
<td>and cyanotic heart disease upon UFH response</td>
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<td>- 100 unit/kg UFH caused a 3-fold increase in ACT values within 15mins of UFH, this reduced to 2-fold increase by 60mins post bolus.</td>
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<tr>
<td>Andrew at al 1994(42)</td>
<td>Prospective</td>
<td>n=65 (Male = 38) Venous thrombosis n=38 Arterial thrombosis n=11 Congenital heart disease prophylaxis n=24</td>
<td>&lt;1 year= 29, 1-10yrs =14, &gt;10yrs= 22</td>
<td>Mean dose according to age:</td>
<td>- UFH effect measured using aPTT</td>
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<tr>
<td></td>
<td>cohort</td>
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<td>&lt;1year 28units/kg/hr &gt;1year 20-22units/kg/hr</td>
<td>- aPTT therapeutic in 68% of patients by 24hrs and 81% of patients by 48 hrs following UFH initiation.</td>
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<td>- Therapeutic aPTT levels achieved in 43% of tests</td>
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<td>Grady, Eisenberg</td>
<td>Prospective</td>
<td>n=36 Children undergoing cardiac angiography.</td>
<td>1 month – 19.5years</td>
<td>50 or 100 units/kg bolus</td>
<td>- UFH effect measured using ACT</td>
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<td>and Bridges 1995(43)</td>
<td>cohort</td>
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<td>- 50units/kg bolus increased ACT to 209±32secs versus ACT of 270±57 secs following a 100units/kg bolus.</td>
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<td>- ACT &gt;200seconds prevented significant increase in thrombin activity, as measured by fibrinopeptide A.</td>
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<td>Saxena et al 1997(44)</td>
<td>Quasi-</td>
<td>N=366 Children undergoing cardiac angiography</td>
<td>17days to 11 years</td>
<td>- 50 units/kg vs 100units/kg.</td>
<td>No information re anticoagulant therapy monitoring was provided.</td>
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<td></td>
<td>experimental</td>
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<td>- Arterial thrombosis rate was 9.8% and 9.3% respectively.</td>
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<td>- Likelihood of thrombosis related to increased number of vascular access attempts (p&lt;0.001), absence of back bleed at the end of procedure (p&lt;0.001) and increased duration of procedure (p&lt;0.01).</td>
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<td>Codispoti et al 2001(45)</td>
<td>RCT of standard UFH therapy for Cardio-pulmonary bypass versus individualized approach</td>
<td>13 in each arm</td>
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<td>- Based on clinical criteria, the authors conclude that 50units/kg is as efficacious as 100units/kg.</td>
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<td>- “Standard” UFH dose was 300units/kg.</td>
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<td>- Interventional UFH dose was individualized based on an automated protamine titration assay</td>
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<td>- Higher UFH doses were given to the intervention group versus the standard therapy group (p&lt;0.001).</td>
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<td>- Blood loss and transfusion requirements lower in intervention vs control group (p=0.05)</td>
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<td>- UFH concentration was measured using an automated protamine titration assay.</td>
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<td>- UFH effect was measured using thrombin generation and fibrinolysis.</td>
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<td>- Thrombin generation (p=0.02) and fibrinolysis (p=0.05) was reduced more significantly in the intervention versus control group.</td>
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<tr>
<td>Chan et al 2002(46)</td>
<td>In vitro spiking of pooled plasma from cord, children and adults</td>
<td>10 donors were used to make up each of the 3 age-related plasma pools</td>
<td>2 to 13 years</td>
<td>0.25units/mL spiked into plasma pools</td>
<td>UFH effect measured using thrombin generation.</td>
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<td>- UFH effect measured using thrombin generation.</td>
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<td>- Thrombin generation demonstrated UFH inhibits thrombin to a greater degree in plasma pools from children compared to adults.</td>
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<td>- Proportionately more thrombin-alpha2M complexes were formed in plasmas from children and newborns compared to that of adults</td>
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<td>Massicotte et al 2003(47)</td>
<td>Multi-centre international RCT of UFH/VKA versus LMWH for venous thrombosis</td>
<td>LMWH = 36 UFH/VKA = 40</td>
<td>4 months to 17.7 years</td>
<td>12.5 % rate of major bleeding reported in UFH/VKA arm versus 5.65% in LMWH arm (ns). (No details provided as to whether these events occurred on UFH or VKA therapy).</td>
<td>No measures of UFH effect were reported.</td>
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<td>- UFH dosing not prescribed as standard practice at each study site was used.</td>
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<tr>
<td>Nankervis et al 2007(48)</td>
<td>Prospective cohort study</td>
<td>12 neonates on veno-arterial extracorporeal membrane oxygenation</td>
<td>Age range not given.</td>
<td>Mean UFH infusion rate 42.2±10.9 units/kg/hr (range 20-69.5units/kg).</td>
<td>UFH effect measures using ACT and anti-Xa assay.</td>
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<td></td>
<td>- UFH effect measures using ACT and anti-Xa assay.</td>
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<td>- mean ACT = 167 ±20 seconds.</td>
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<td>- mean anti-Xa assay = 0.73±0.19units/mL.</td>
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<td>- poor correlation between ACT and UFH dose and ACT and anti-Xa assay</td>
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<tr>
<td>Author/date</td>
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</table>
| Baird et al 2007(49) | Retrospective review of Extracorporeal Membrane Oxygenation at a single institution between 1980-2001 | Children requiring ECMO (duration ranged from 6-134 hours) | Median age 3 days (IQR 1-52 days) | - Mean UFH dose= 45± 21 units/kg
- Survivors (49±20 units/kg/hr) received higher UFH doses than non-survivors (39±22 units/kg/hr) (p<0.001). | - UFH effect measured using ACT
- Mean ACT 227±50 secs.
- Modest correlation between UFH dose and ACT (r=0.48 survivors; 0.42 non-survivors).
- All survivors had shorter ECMO times (171± 24 hours versus 197±166 hours, p = 0.017)
- ACT not predictive of survival (p=0.36) |
| Kuhle et al 2007(50) | Prospective cohort study | Children >36 weeks gestational age and ≤18 years of age admitted to the critical care unit and requiring therapeutic doses of UFH for ≥12h | Age data not given | Mean dose 25.3± 8.4 units/kg/hr | - UFH effect measured using aPTT, anti-Xa and TCT.
- No assay demonstrated strong correlation with UFH dose.
- ‘Agreement’ between APTT and aXa occurred in <33% of cases.
- Based on the assumption that the anti-Xa is the ‘gold standard’ method for UFH monitoring, the authors concluded the aPTT was a poor option for UFH monitoring |
| Guzzetta et al 2008(51) | RCT of standard UFH or UFH titrated to HEPCON during Cardio-Pulmonary Bypass | Infants requiring CPB who were < 6 mo of age | Infants in intervention were older than control group (114± 29 days vs 138±27 days; p= 0.04) | - Intervention group received significantly higher UFH doses than control 597± 22 vs 108± 32 units; p<0.001)
- No difference in the mean protamine dose in each arm (control= 4.0±0mg/kg; intervention=3.9±1.9 mg/kg; P< 0.84). | - UFH effect measured using surrogate measures: Prothrombin Fragments 1.2, fibrinopeptide A, βTG, FV, FVIII.
- Authors concluded that use of the Hepcon resulted in greater suppression of haemostasis than standard UFH dosing regimen |
<p>| Ignjatovic et al 2006 (52) | In vitro UFH spiking study | Plasma pools consisting of at least 15 donors were | &lt; 1 year 1-5 years | UFH spiked in concentration of 0.1, 0.3, 0.5, 0.7, 1.0 units/mL | - UFH effect measured using aPTT, anti-Xa, anti-IIa |</p>
<table>
<thead>
<tr>
<th>Author/date</th>
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<tbody>
<tr>
<td>Ignjatovic et al 2006 (53)</td>
<td>Prospective observational study</td>
<td>167 patients (96 male) Paediatric Intensive Care Unit Haemodialysis unit Cardiac angiography</td>
<td>Mean age = 2.2 ±3.1 years (range 2 days to 13.5 years).</td>
<td>UFH dosing ranged from 10units/kg/hr infusion to 100units/kg bolus dose</td>
<td>- An anti-Xa assay of 0.35 to 0.7 units/mL resulted in aPTT ranges of 82-177secs in infants &lt; 1 yr to 55-118 in adults (p&lt;0.05). - UFH effect measured using aPTT and anti-Xa assay. - In vivo response of aPTT to UFH is age-dependent. - aPTT values correlating to an anti-Xa assay of 0.35 to 0.7 units/mL were &gt;180seconds. - aPTT values correlating with anti-Xa assay of 0.35 to 0.7units/mL demonstrated clinically significant variance.</td>
</tr>
<tr>
<td>Ignjatovic et al 2007(54)</td>
<td>Prospective observational study</td>
<td>Children admitted to the Pediatric Intensive Care Unit or Haemodialysis unit requiring UFH therapy</td>
<td>UFH dose of 10units/kg/hour to 25units/kg/h (± bolus) within the previous 6 h</td>
<td>- UFH effect measured using 3 different anti-Xa assay kits. - anti-Xa assay kits with exogenous antithrombin or Dextran Sulphate produce difference anti-Xa results compared to the modified assay that contained neither. - The addition of AT or DS to anti-Xa kits generates non-physiological results.</td>
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<tr>
<td>Newall et al 2009(55)</td>
<td>Prospective observational study of UFH in PICU setting.</td>
<td>N=85 Patiens &lt; 16years</td>
<td>54 (64%) &lt; 1yr. Remaining patients analysed according to age (1-5,6-10, 11-16years)</td>
<td>UFH infusions of &gt;10units/kg/hr. UFH doses ranged from 12.1 to 15.1units/kg/hour.</td>
<td>- UFH effect measured using aPTT, anti-Xa, anti-IIa, and thrombin generation. - Antithrombin levels decreased compared to age-related norms in children up to 11 years of age. - anti-Xa and anti-IIa showed a trend to lower levels in younger children despite similar UFH doses. - thrombin generation showed a trend for increased thrombin inhibition in older children. -in vitro AT supplementation did not correct the age-related differences in anti-Xa or ETP.</td>
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</table>

Table 1. Summary of Studies Investigating UFH Dosing, Administration and Monitoring in Infants and Children
c. Monitoring of UFH

Monitoring of UFH is necessary due to its relatively narrow therapeutic window. Sub-therapeutic levels of UFH are associated with an increased risk of thrombus development, propagation or recurrence, whilst supra-therapeutic UFH levels are associated with a significant bleeding risk (56). Despite the enormous energy and funding that has been invested in the development of laboratory assays that will inform clinicians regarding UFH therapy, all assays currently available share two common limitations: first, the heterogeneity of UFH has prohibited the development and utilization of one method suitable for measuring UFH effect universally; second, measures of UFH effect in vitro are yet to mirror UFH effect in vivo. As such, the results generated aim to correlate with the goal of thrombosis treatment or prevention, and do not measure the primary goal of therapy.

Table 2 summarises the 3 assays commonly used to monitor UFH therapy. The gold standard method for measuring UFH concentration in plasma is Protamine titration. In 1954, Refn and Vestergaard reported a method for protamine titration to determine UFH concentration, which is still used today (57), although a micro-method has been published that allows this assay to be performed using one fifth of the original plasma volume (58). Recommendations for UFH therapy from the American College of Chest Physicians (ACCP) suggest target APPT ranges for UFH therapy reflect heparin concentrations of 0.2 – 0.4 IU/ml by protamine titration or 0.35 to 0.7 IU/ml by anti-Xa assay (56). The APTT range corresponding to these concentrations of UFH must be determined on an institutional basis due to the high level of variability observed between APTT reagents (59). Protamine titration produces reliable and reproducible results, however it is not a convenient assay for the conventional management of UFH as it is not readily automated (60). This has resulted in many laboratories using the anti-Xa assay as a surrogate measure of UFH concentration. The anti-Xa assay facilitates the measurement of UFH’s AT-catalysed inhibition of Xa (59-66) and is broadly used to guide the determination of therapeutic APTT ranges in the clinical management of UFH (56). The anti-Xa assay is easy to perform, automated and experiences minimal interference from biological variables, however it is more expensive than the commonly used APTT and may not be available in smaller laboratories (60). Prior to performing an anti-Xa assay, each laboratory must create a normal curve for UFH using a pool of normal plasma spiked with varying amounts of UFH. To this plasma pool, known quantities of Xa are added, and after a period of incubation, the amounts of residual Xa are measured (59).

The APTT can best be described as a non-specific measure of the intrinsic and common pathways of the coagulation system (67). Clinical trials of UFH therapy investigating mode of delivery (68), duration of therapy (69) and dose (70) determined that a heparin concentration of 0.2-0.4 units/ml by protamine titration that correlated to an APTT of 1.5 to 2.5 times normal values produced desirable UFH safety and efficacy outcomes (71, 72). As a result, most advisory bodies recommend therapeutic APTTs be determined by correlating APTT results with therapeutic UFH levels as measured by anti-Xa assay (0.35-0.7 IU/ml) or protamine titration (0.2-0.4 IU/ml) (56). However, the APTT is sensitive to changes in coagulation factors, inhibitors to coagulation factors, and pre-analytical variables such as difficult venous bleed, delayed mixing with citrate solution and delayed time to laboratory processing (59, 61, 73, 74). As a result, the APTT lacks specificity for UFH therapy (75). Despite these limitations, the APTT continues to be widely utilized in UFH management.
In paediatric populations, baseline APTT levels are increased compared with adult normative values and alter with age. This likely reflects quantitative, and possibly qualitative, developmental differences in various haemostatic parameters. Whilst clinical trials confirmed the need for substantive prolongation of the APTT, anti-Xa and/or protamine titration assays for the effective management of thromboembolic disease in adults, such trials have not been conducted in paediatric populations. As such, the defined laboratory parameters that suggest UFH is likely to be safe and efficacious in adult patients remain as yet untested in paediatrics. What is abundantly clear however is that unfractionated heparin appears to elicit variable effect in infants and children, compared to adults (52, 53, 76, 77). Use of either a protamine titration assay range of 0.2 to 0.4 unit/mL or an anti-Xa assay range of 0.35 to 0.7 units/mL results in a 3 to 4-fold increase in APTT prolongation than that observed in adults(76, 77). Whether titrating UFH therapy to achieve an APTT in excess of 200 seconds in a child would produce improved therapeutic outcomes without significantly increasing haemorrhagic risk is not known.
<table>
<thead>
<tr>
<th>Assay</th>
<th>Common Uses</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT F-Clot</td>
<td>- Coagulation screening assay</td>
<td>- Low cost.</td>
<td>- Prolonged APTT does not mean effective anticoagulation</td>
</tr>
<tr>
<td></td>
<td>- Therapeutic UFH monitoring</td>
<td>- Easy to perform</td>
<td>- Wide variability in reagent sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Non-physiological measure of UFH effect</td>
</tr>
<tr>
<td>Anti-Xa F-Ch</td>
<td>- Calibration of APTT reference ranges.</td>
<td>- Direct measure of UFH inhibition of Xa.</td>
<td>- Not as broadly available as APTT.</td>
</tr>
<tr>
<td></td>
<td>- Therapeutic UFH monitoring.</td>
<td>- Easy to perform</td>
<td>- Costs more than the APTT.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Some variability in reagent sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Does not measure other mechanisms of UFH effect (e.g. Anti-IIa).</td>
</tr>
<tr>
<td>Protamine Titration Q</td>
<td>- Not used clinically.</td>
<td>- Only assay that directly measures UFH concentration.</td>
<td>- Not broadly available.</td>
</tr>
<tr>
<td></td>
<td>- Used by reference laboratories.</td>
<td>- Inexpensive.</td>
<td>- Automated methods have not been validated for management of therapeutic UFH and manual methods labor intensive.</td>
</tr>
</tbody>
</table>

Table 2. Summary of Assays Used to Monitor UFH Therapy.
Key: F-Clot = Functional, Clot based assay; F-Ch = Functional, Chromogenic assay; Q = quantitative assay
d. **UFH-related Adverse events**

**Bleeding**

As with all studies reporting bleeding outcomes of anticoagulant therapy, determining the true incidence of clinically significant bleeding from UFH trials is complicated by the lack of consistency in defining bleeding events. As a result, a broad range of major bleeding events associated with UFH therapy have been reported, ranging from 1% to 56% of patients receiving UFH therapy (69, 78-81). Generally, bleeding rates reported with UFH therapy increase in the presence of individual risk factors, significantly prolonged or increased monitoring assays (APTT, anti-Xa assay) and method of administration(81).

In the only prospective cohort study of UFH therapy in paediatrics, no major bleeding events were observed(82). However, this finding must be viewed in context of the relatively low rate of therapeutic anticoagulation reported in the study (68% at 24 hours) and the likelihood of patients who did not have a therapeutic APTT being sub-therapeutic. In the only randomised controlled trial of therapeutic anticoagulation that has been conducted in children, (the REVIVE study) low molecular weight heparin therapy was compared to UFH and VKA for the treatment of venous thromboembolic events(47). The REVIVE study reported a major bleeding rate of 12.5% in the UFH/VKA arm of the study(47). A recent retrospective cohort study of children receiving UFH in a paediatric intensive care unit setting determined that 24% of children exposed to UFH development major bleeding(83). Whilst alarming, this result must be tempered by the very broad definition of major bleeding used within the study.

**Heparin-Induced Thrombocytopenia (HIT)**

Heparin Induced Thrombocytopenia II (HIT II) is an immune-mediated adverse reaction to UFH that occurs in less than 3% of patients exposed to heparin for 5 or more days(84). Diagnosis of HIT II is complicated by the lack of any a definitive diagnostic test to confirm the presence of an immune reaction to UFH. There are two methods of testing for HIT II: functional assays (platelet aggregation/ Serotonin-release assay) and immuno-assays (PF4 ELISA)(85). Both methods offer a high negative predictive value (i.e. rule out HIT II) however their positive predictive value is moderate(85).

There have been no prospective studies to determine the incidence of HIT in paediatrics. There are a number of case reports which highlight the paediatric-specific nature of this adverse-drug reaction, but their methods of confirming the diagnosis of HIT and management of the adverse reactions are inconsistent. Platelet aggregation studies have been frequently used to investigate the prevalence of HIT in children exposed to UFH (86). Whilst such assays do measure reactivity of platelets to heparin, this reactivity does not necessarily indicate the presence of an immune reaction to heparin and cannot be used to confirm the diagnosis of HIT alone. One tertiary paediatric centre conducted a retrospective audit of all suspected cases of HIT in that centre(87). Despite 15% of children admitted to that centre being exposed to UFH, only four cases of suspected HIT were identified across a 2-year period. This finding confirms the suspicion of many paediatric haematologists that HIT occurs with significantly less frequency in children than in adults.
Accidental UFH Overdose

Given the many different preparation of UFH available (see formulary), accidental overdose of UFH is a significant risk. There is no universally recognized mechanism to aid in the correct identification of different strength vials. For infants especially, confusing a 50 unit/5mL vial with a 5000 unit/5mL vial can easily occur as the only difference between the two is the colour of the writing on the vial. Great care therefore needs to be paid when preparing all UFH infusions or bolus doses.

e. Formulary of UFH

Unfractionated heparin is prepared by many pharmaceutical companies. The strength and volume of vials varies significantly and as previously mentioned, there is no consistent approach to packaging UFH doses. Available strengths range from 5 units/1mL to 500 units/mL.

f. UFH Summary recommendations

(i) UFH is an affordable medication and the laboratory assays available to monitor it are readily available and affordable. Of the available assays suitable for monitoring UFH therapy, the aPTT, whilst having acknowledged limitations, is certainly the most affordable option.

(ii) Age-specific dosing of UFH is required. All dosing decisions need to be reviewed in light of laboratory-based monitoring to optimize treatment outcomes. Evidence-based guidelines for UFH dosing and administration are best taken from the ACCP Antithrombotic Therapy guidelines(6). Many of the clinical recommendations listed within these guidelines however may not reflect the patient demographics common to developing nations.

(iii) None of the laboratory assays currently available for UFH monitoring demonstrate strong correlation with protamine titration – the gold standard method of determining UFH concentration. As a result, all laboratory assay results should be considered in light of the patient’s clinical condition and prognosis.

Vitamin K antagonists (VKAs)

a. Mechanism of action and pharmacology

Warfarin, phenprocoumon and acenocoumarol are Vitamin K antagonists. Bacteria in the gut are responsible for the reduction of Vitamin K to Vitamin K epoxide. This is absorbed in the intestine and converted to available Vitamin K by an enzyme known as Vitamin K epoxide reductase. Clotting factors II, VII, IX and X need this enzyme to become functional. Vitamin K Antagonists exert their action by inhibiting Vitamin K epoxide reductase, reducing the amount of Vitamin K available to synthesise the Vitamin K dependent clotting factors (88, 89, 90 10). Antagonism of Vitamin K, or a deficiency of this vitamin results in effective anticoagulation of the patient (90, 91). Therapeutic doses of VKA drugs reduce the availability of functional Vitamin K dependent clotting factors by approximately 30% (90). Upon oral ingestion, VKAs are absorbed rapidly from the GI tract and bind firmly to plasma albumin (92). The
VKA are primarily metabolised by the liver, raising significant clinical implications for patients with hepatic dysfunction due to their reduced ability to clear the drug (89, 91, 93).

The anticoagulant state produced by VKAs is dependent upon clearance of functional clotting factors from the body. Factor VII has the shortest half-life of all the Vitamin K dependent clotting factors and it is the first factor affected by the initiation of VKA therapy. Factor II (prothrombin) has a much longer half-life and levels of Factor II do not decrease until day five to six of therapy. The reduction in circulating Factor VII levels is not thought to be as significant in producing an antithrombotic state as the reduction in Factor II (92). Although certain coagulation studies may become prolonged after two to three days of therapy, achievement of functional anticoagulation is not fully achieved until day five to six of therapy (90).

b. Dosing and administration

The dose response relationship of VKA therapy is influenced by both genetic and environmental factors. Genetic resistance to VKAs has been reported in human and animal models. Environmental factors such as coexisting disease states, concomitant medications, and diet also influence VKA response (89, 91, 92). Medications such as aspirin and non-steroidal anti-inflammatories, although not directly influencing VKAs, do increase the risk of bleeding secondary to VKA therapy by disrupting normal platelet function (92). The response to VKA therapy can fluctuate significantly secondary to changes in the factors described previously. Patients receiving VKAs must be closely monitored in order to prevent adverse events such as haemorrhage or progressive thromboembolic disease, which are directly related to “over” and “under” anticoagulation respectively (89).

Original research studies reporting evidence related to the dosing, administration and/or monitoring of VKA therapy in children was identified from a Medline search (1950-2009). Three searches were conducted:

i). “Warfarin”: limited to ‘Administration and Dosing’, ‘English Language’, ‘Humans’ and ‘All Child’ (0-18years). Seventeen papers were identified, but of these only seven papers provided details regarding warfarin dosing and/or monitoring in children.

ii). “Phenprocoumon”: limited to ‘Administration and Dosing’, ‘English Language’, ‘Humans’ and ‘All Child’ (0-18years). Eight papers were identified, however no papers provided details regarding phenprocoumon dosing and/or monitoring in children.

iii). “Acenocoumarol”: limited to ‘Administration and Dosing’, ‘English Language’, ‘Humans’ and ‘All Child’ (0-18years). Twenty-one papers were identified, however only two papers provided details regarding acenocoumarol dosing and/or monitoring in children.

Table 3 summarises the evidence generated by these studies.
<table>
<thead>
<tr>
<th>Author/date</th>
<th>Study design</th>
<th>Study population (incl. N)</th>
<th>Age Distribution</th>
<th>Dosing recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Bradley et al 1985(94)| Comparative Cohort study of warfarin and Aspirin/dipyridamole | N= 28 Children with prosthetic heart valves. | Mean age = 7.9 years              | - Mean warfarin dose = 0.16mg/kg/day.  
- Mean aspirin/dipyridamole doses = 6.1 and 1.9 mg/kg/day, respectively       | - No monitoring data reported  
- Haemorrhage risk 22/100 pt years on warfarin vs 0/100 pt years on Aspirin/Dipyridamole.  
- Thrombosis risk 0/100 patient years on warfarin vs 12/100 pt years on ASA/Dip.  
- Authors concluded that warfarin is better than Aspirin/Dipyridamole for prosthetic valve prophylaxis as the morbidity and mortality outcomes of thrombosis were worse than those associated with bleeding. |
| Doyle et al 1988(95)  | Retrospective and prospective cohorts | Retrospective n=26 Prospective n=15 | Not specified                      | Warfarin Loading Dose = 0.2mg/kg/day for 2 days                                         | Warfarin monitored using the Prothrombin time |
| Andrew et al 1994(96) | Prospective cohort               | n=115 (68 males) 2° prophylaxis = 56 1° prophylaxis = 59 Venous thrombosis = 64 Congenital Heart Disease =67 | < 1 year (19) 1-5 years (33) 6-10 years (20) 11-18 years (43) | Mean warfarin dose (mg/kg±SD): <1 year = 0.32 ± 0.05mg/kg 11-18 years = 0.09 ± 0.01mg/kg | - Warfarin monitored using the INR  
- Mean INR frequency = 4 tests/mth  
- Target therapeutic range (2.0 – 3.0) Achievement = 46% (n=101) |
| Tait et al 1996(97)   | Prospective cohort               | n=45 (27 males) Main indication: CHD | 9 months to 18 years               | Median warfarin dose mg/kg/day (IQR): < 2yrs 0.14 (0.11-0.19) 2-5yrs 0.11 (0.09-0.13) 6-10yrs 0.09 (0.07 – 0.1) 11-18yrs 0.08 (0.07-0.09) | - Warfarin monitored using the INR  
- Mean INR frequency was every 3 weeks  
- TTR Achievement  
  - TTR 2.0 – 3.0: 62%  
  - TTR 3.0 – 4.0: 39% |
| Cheung & Leung 1998(98)| Retrospective cohort            | n= 35 (23 male) DVT = 2 CHD = 33 | Mean age 8.4 ± 5.8 years (range: 0.4 to 19.7 years). | - Warfarin Target INR 1.5 to 2.5  
- Mean warfarin dose (mg/kg±SD): 0–2 years = 0.14±0.05 2–5 years = 0.13±0.04 5–10 years = 0.09±0.04 10–18 years = 0.07±0.03 | - Warfarin monitored using the Prothrombin time expressed as INR.  
- Frequency of testing not specified  
- TTR Achievement not specified |
| Streif et al 1999(99) | Prospective cohort               | n=319 (180 males) Secondary prophylaxis=41% | <1 year 43 1-6 years 123 | - Mean warfarin dose (mg/kg±SD): <1year = 0.33±0.2 | - Warfarin monitored using the INR.  
- Mean No. of INR tests/month ± SD; TTR%±SD |
Table 3. Summary of Studies Investigating VKA Dosing, Administration and Monitoring in Infants and Children

<table>
<thead>
<tr>
<th>Author/date</th>
<th>Study design</th>
<th>Study population (incl. N)</th>
<th>Age Distribution</th>
<th>Dosing recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonduel et al 2003(102)</td>
<td>Prospective cohort</td>
<td>n=93 (54 males)</td>
<td>Primary prophylaxis =21</td>
<td>Acenocoumarol doses: 2mth-1 year = 0.2 mg kg(^{-1})</td>
<td>Acenocoumarol monitored using the INR - Median No. of INR tests/mth; TTR% 2months-1 year = 3; 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary prophylaxis =72</td>
<td>1-5 years = 0.09 mg kg(^{-1})</td>
<td>1-5 years = 2; 57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Venous thrombosis = 66</td>
<td>6-10 years = 0.07 mg kg(^{-1})</td>
<td>6-10 years = 2; 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pulmonary embolism = 5</td>
<td>11-18 years = 0.06 mg kg(^{-1})</td>
<td>11-18 years = 2; 63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHD = 22</td>
<td>Median (range) = 5.1 years (0.2-18)</td>
<td></td>
</tr>
<tr>
<td>Soper et al 2006(101)</td>
<td>Retrospective Case Series</td>
<td>n=26 (16 males)</td>
<td>Fontan circulation =14</td>
<td>- No recommendation regarding warfarin dose/kg</td>
<td>- Warfarin monitored using the INR - Median No. INR tests/mth; TTR % for total population = 1.9–2.1; 76-79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prosthetic valve = 7</td>
<td>- No recommendation regarding warfarin dose/kg/</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Kawasaki disease = 2</td>
<td>- Warfarin monitored using the INR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiomyopathy = 1</td>
<td>- Warfarin monitored using the INR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Other = 3</td>
<td>- Warfarin monitored using the INR</td>
<td></td>
</tr>
<tr>
<td>Woods et al 1986(103)</td>
<td>Retrospective cohort</td>
<td>n=31 (12 male)</td>
<td>CHD with prosthetic heart valves</td>
<td>- No recommendation regarding warfarin dose/kg</td>
<td>- Acenocoumarol Mean dose = 1.5mg/day (0.71-2mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age range 5mths – 16 years.</td>
<td>- Acenocoumarol Mean dose = 1.5mg/day (0.71-2mg/day)</td>
<td>- Acenocoumarol monitored using the Prothrombin time expressed as INR - TTR 72% - Monthly monitoring assays.</td>
</tr>
</tbody>
</table>

Table 3. Summary of Studies Investigating VKA Dosing, Administration and Monitoring in Infants and Children
c. **VKA Monitoring**

The effect of warfarin therapy is measured by the Prothrombin Time (PT). This measurement is achieved by combining the plasma of the anticoagulated patient with thromboplastin derived from rabbit or human brain (and later recombinant thromboplastins), and measuring elapsed time until clot formation. The PT is measured in seconds, with the usual normal range being between 12-16 seconds. In 1982 the World Health Organisation recommended that the INR be used to report the PT to ensure consistency and reliability (90). This ratio is determined by assigning each thromboplastin used in performing a PT a sensitivity index (ISI), which is used to interpret the PT result generated. The INR in a non-warfarinised, healthy adult should be between 0.9-1.1.

Regular blood monitoring of adults and children receiving warfarin is imperative to the safe and effective use of this agent (11, 96, 99, 104-106). The literature supports the current understanding that children receiving warfarin require more frequent monitoring than their adult counterparts due to the complexity of their underlying medical conditions (107). The gold standard method for monitoring warfarin therapy is a venous INR. In the subgroup of paediatric patients likely to be warfarinised, the ability to use the gold standard method of testing is significantly challenged due to poor venous access relative to the frequency of testing required (107).

The advent of point-of-care INR monitoring using a drop of capillary whole blood has provided a safe and reliable alternative to venous INR monitoring in children(100, 107-112). Many of the commercially available capillary INR monitors have had validation studies performed in children, and have been shown to perform equally well when used within institutional settings or by patients in their homes.

d. **VKA-related adverse events**

**Bleeding**

The literature suggests that although more difficult to control in children, warfarin produces a similar risk of bleeding in children as in adults (0.5-6.5% risk of major bleeding per year of therapy)(88, 96). As warfarin therapy is likely to be initiated in children with significant underlying pathologies, the presentation of a bleeding event is likely to occur at a site of injury or weakness, rather than at an unaffected site (113). In the Sixth ACCP guidelines for *Antithrombotic therapy in children*, Monagle et al report the approximate bleeding rates for children receiving warfarin, as minor or serious events (104). Twenty percent will develop a minor bleeding event (eg. bruising, epistaxis, bleeding from cuts etc) per patient year. The annual rate of serious bleeding is proportional to intensity of therapy, (114, 115) with children who have mechanical heart valves (target INR 2.5-3.5) having a higher risk (<3.2%) than all other warfarinised children (target INR 2.0-3.0) in whom the major bleeding rate is 1.7% (104).

**Osteoporosis**

Of recent years, there has arisen concern regarding the long term effects of warfarin on bone mineral density (BMD), particularly in children. A component of warfarin induced embryopathy is deformity in bone development (116). Bone growth requires Vitamin K dependent proteins (osteocalcin), which, like the coagulant proteins produced by the liver, are antagonised by warfarin. No prospective data has been published on this potential adverse event in children. A paper was presented at an
international conference in 1999 suggesting longterm warfarin therapy may influence the BMD in growing children (117). Due to concerns raised in this paper, further research was conducted in an Australian paediatric centre, revealing 94% of children taking long term warfarin had BMD results below their age-related mean, with one third recording a BMD score two standard deviations below the mean (118). The authors acknowledge that confounding variables exist as to the cause of this reduced BMD, notably the prevalence of congenital heart disease in this population. In the adult literature, conflicting reports exist as to the relationship between warfarin and reduced bone density (119, 120).

e. **VKA Formulary**

No suspension formulation of VKAs is available. All presentations are in tablet form.
*Coumadin*: 1mg/ 2mg/ 5mg
*Marevan*: 1mg/ 3mg/ 5mg
*Phenprocoumon*: (not available in Australia and i’m not sure what the presentations available internationally are)

f. **Summary recommendations for VKAs**

Vitamin K antagonists have been shown to produce safe and effective anticoagulation in children in both retrospective and prospective cohort studies. Due to the lack of randomized trials in this area however, data is lacking regarding optimal dosing strategies and target therapeutic ranges for listed indications in children. As such, the bulk of recommendations regarding VKA therapy in children have been extrapolated from adult evidence. A summary of these recommendations can be found in the ACCP Recommendations for Antithrombotic Therapy in Children(6).

More evidence is available regarding the optimal dosing and monitoring of warfarin and acenocourmarol in children than phenprocoumon. Choice between warfarin and acenocoumarol should be made based upon geographical availability and experience. Both require monitoring using a prothrombin time reported as an INR. Given the lack of paediatric-specific evidence regarding optimal treatment intensity and duration, extrapolation from adult indications and practice is common. Vitamin K antagonists are inexpensive drugs and the monitoring assays used to measure treatment efficacy are affordable when venous blood collection is performed. The infrastructure required to support point-of-care monitoring of VKA therapy is more costly.
Low Molecular Weight Heparins

a. Mechanism of action and pharmacology

Low Molecular Weight Heparins are prepared by chemically or enzymatically altering UFH chains to isolate the region containing the unique pentasaccharide sequence required for binding to antithrombin(121). As a result, LMWHs experience less competitive plasma binding compared to UFH and elicit a more predictable anticoagulant response(6, 121, 122). Due to their reduced chain-length, LMWHs are unable to bind simultaneously to antithrombin and thrombin, meaning thrombin inhibition is not possible(121). Rather, LMWH preparations produce the bulk of their anticoagulant effect by potentiating the antithrombin-mediated inhibitor of factor X(121).

This chemical alteration results in LMWHs having a longer half-life and reduced reversibility compared to UFH(6). As a result, LMWHs are commonly used in patients with less acute risk of haemorrhage and for whom prompt reversibility is unlikely to be necessary.

b. Dosing and administration

Original research studies reporting evidence related to the dosing, administration and/or monitoring of LMWH therapy in children was identified from a Medline search (1950-2009). The key search term was “Low Molecular Weight Heparin” with resultant articles limited to ‘Administration and Dosing’, ‘English Language’, ‘Humans’ and ‘All Child’ (0-18years). Eight papers provided details regarding low molecular weight heparin dosing and/or monitoring in children. These are summarized in Table 4.
<table>
<thead>
<tr>
<th>Author/date</th>
<th>Study design</th>
<th>Study population (incl. N)</th>
<th>Age Distribution</th>
<th>Dosing recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Hofmann et al 2001(123) | Retrospective cohort study | N=79 children Primary thromboprophylaxis post surgery or trauma = 62 Venous thrombosis = 13 78% had LMWH for < 2 wks Enoxaparin or nadroparin were used. | 2 weeks to 19 years. | - LMWH doses of 45-100 units/kg/day required to achieve prophylactic anti-Xa levels of 0.2-0.4 units/mL.  
- No patient receiving the above regime developed a new thrombosis.  
- LMWH doses of 200-500 units/kg/day required to achieve therapeutic anti-Xa levels of 0.5-1.0 IU/mL.  
- Clinical outcomes all improved in children given LMWH following lytic therapy, regardless of whether lytic therapy resulted in complete thrombus resolution or not.  
- Patients given LMWH following UFH demonstrated either complete (n=6), partial (n=2) or no re-occlusion (n=4). | - LMWH monitored using the “Coacute” anti-Xa assay used (Chromogenix), containing exogenous antithrombin. |
| Strater et al 2001(124) | Quasi-experimental design comparing Aspirin and LMWH | N= 135 children post first episode of ischaemic stroke. Aspirin n=49 LMWH n=86 Follow up 8-48 months | Age range 6 months to 18 years | - Aspirin dose = 4 mg/kg per day.  
- LMWH dose = 1 to 1.5 mg/kg per day  
- 9.6% of children had a recurrent stroke – there was no difference in incidence rate between Aspirin and LMWH arms. | - LMWH measured using an anti-Xa assay with target range 0.2-0.4 units/mL.  
- No data given re whether this was achieved in the arm allocated LMWH treatment. |
| Chan et al 2002(125) | In vitro spiking of pooled plasma from cord, children and adults | 10 donors were used to make up each of the 3 age-related plasma pools | 2 to 13 years | 0.25 units/mL spiked into plasma pools | - LMWH effect measured using Thrombin generation.  
- Thrombin generation demonstrated LMWH inhibits thrombin to a greater degree in plasma pools from cord blood compared to children and adults.  
- More thrombin-alpha2M complexes were formed in plasma from children and newborns compared to adults |
| Massicotte et al 2003(126) | Dose finding study of LMWH primary prophylaxis of | N=24                                                                 | 3 months to 16 years. | - Children > 5 kg require 30 units/kg (SC), twice daily  
- Children < 5 kg require 50 units/kg (SC), twice daily. | - LMWH monitored using an anti-Xa assay.  
- Dosing changes made using a nomogram to reflect an anti-Xa assay of 0.1-0.3 units/mL. |
<table>
<thead>
<tr>
<th>Author/date</th>
<th>Study design</th>
<th>Study population (incl. N)</th>
<th>Age Distribution</th>
<th>Dosing recommendation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massicotte et al 2003(47)</td>
<td>Multi-centre international RCT of UFH/VKA vs LMWH for VTE</td>
<td>36 in LMWH arm 40 in UFH/VKA arm</td>
<td>4 months to 17.7 years</td>
<td>- A nomogram was used to adjust LMWH doses to achieve an anti-Xa level between 0.50 and 1.0 units/ml. - Major bleeding occurred in 5.6% of patients in the LMWH arm.</td>
<td>- LMWH effect was measured using an anti-Xa assay 4 hours post a morning dose on either Day 1 or 2 of treatment. - Once TTR anti-Xa achieved, tests were repeated monthly. - Anti-Xa assay were within TTR for 75% of test points.</td>
</tr>
<tr>
<td>Massicotte et al 2003(127)</td>
<td>Multi-centre international RCT of LMWH vs Placebo for prevention of CVL-related thrombosis</td>
<td>N=186 Children having CVL insertion. N=92 reviparin N=94 standard care</td>
<td>2 months to 16.8 years</td>
<td>- Treatment arm received 30 units/kg for infants and children &gt;3 months of age and 50 units/kg if &lt; 3 months of age, twice daily - Control group received no anticoagulation. - Study was underpowered, but found no significant difference in rate of CVL-related thrombosis between the 2 arms (14.1% vs 12.5% (OR=1.15; 95% CI 0.42, 3.23).</td>
<td>- LMWH effect measured using anti-Xa assay. - Mean (range) anti-Xa results in LMWH arm: 0.136 (0.025–0.550) units/ml.</td>
</tr>
<tr>
<td>Kuhle et al 2005(128)</td>
<td>Single centre, open label, phase II study.</td>
<td>N=35</td>
<td>Age groups: - 0-2 months - 2 month-1 year - 1-5 years - 6-10 years - 11-16 years</td>
<td>- Younger children required increased doses of Tinzaparin compared to older children. - Younger children cleared Tinzaparin more rapidly and had increased volume of distribution compared to older children. - Up to 75% of &lt;1yrs olds had subtherapeutic anti-Xa assays</td>
<td>- LMWH was monitored using an anti-Xa assay. - Infants required anti-Xa monitoring at least twice monthly. - Younger children achieved earlier peaks in anti-Xa activity compared to older children.</td>
</tr>
<tr>
<td>Schobess et al 2006(129)</td>
<td>Open label pilot safety study</td>
<td>N=80 Infants and children with venous thrombosis. Outcome measures: Post Thrombotic Syndrome, recurrent thrombosis, bleeding and death.</td>
<td>Age range 3 months to 18 years</td>
<td>- LMWH Dose given was 1mg/kg BD for 7-14 days after which patients were stratified to receive once daily (1.5mg/kg) or BD (1 mg/kg BD) dosing.</td>
<td>- LMWH monitored using an anti-Xa assay. - Target anti-Xa assay 4 hours post dose = 0.5-0.8 units/mL. 3 patients required dose adjustments based on sub- or supra-therapeutic anti-Xa levels.</td>
</tr>
</tbody>
</table>

Table 4. Summary of Studies Investigating LMWH Dosing, Administration and Monitoring in Infants and Children
c. Monitoring

Low molecular weight heparin therapy is monitored using the anti-Xa assay. The therapeutic range for LMWH management of thromboembolic disease is an anti-Xa assay between 0.5 and 1.0 unit/mL (6, 121, 122, 130). An anti-Xa range of 0.3 to 0.5 units/mL is considered an acceptable range for the prevention of thromboembolic disease (6, 121, 122, 130). The anti-Xa assay can be purchased as a test kit from a number of providers and is performed via an automated coagulation analyser.

The anti-Xa assay requires venous collection into a citrate containing tube. There are currently no point-of-care devices validated for use in monitoring LMWH therapy. Recent evidence has demonstrated that LMWH has a less consistent dose-response profile in children compared to adults (122, 131). As a result, ongoing monitoring of LMWH therapy is necessary even once steady-state therapy appears to have been achieved. Given the increased expense of anti-Xa monitoring compared to the APTT assay, and the fact that not all institutions are able to perform this assay, consideration must be given to the availability of monitoring prior to choosing a LMWH as a therapeutic option.

d. Adverse events

Bleeding

Major bleeding is the most serious potential adverse event associated with LMWH therapy in children. Rates of LMWH-related major bleeding range from 0.7% to 5.6% in children (47, 122), with one study including only neonate participants reporting a major bleeding rate of 10.8% (132). Bleeding is more commonly reported in infants and children who have had recent injury or surgery (6).

Other

There is no paediatric-specific data regarding the potential association between LMWH preparations and heparin induced thrombocytopaenia, osteoporosis or allergy.

e. Formulary

Paediatric dose-finding and pharmacokinetic studies have been conducted for Enoxaparin, Tinzaparin and Reviparin.

Australia

Enoxaparin: 20mg/0.2mL; 40mg/0.4mL; 60mg/0.6mL*; 80mg/0.8mL*; 100mg/1.0mL*; 120mg/0.8mL*; 150mg/1.0mL* (*graduated syringes)
Dalteparin: 2500units/0.2mL; 5000units/0.2mL; 7500units/0.75mL; 10,000 IU/mL; 12500units/0.5mL; 15000units/0.6mL; 18000units/0.72mL
Danaparoid: 750units/0.6mL

f. Summary recommendations

Low Molecular Weight Heparin preparations provide an attractive alternative to UFH and VKA, both of which require frequent blood monitoring. That being said, LMWH still require venous blood collection for anti-Xa monitoring even once therapeutic levels have been achieved. This is due to the fact that children have a less predictable dose-response to LMWH preparations than adult patients. As such, access to anti-Xa monitoring is essential.
Low molecular weight heparin preparations and the anti-Xa assays required to monitor them make choosing LMWHs a more expensive option than either UFH or VKAs.

4. **Summary**

Anticoagulant therapies are reportedly being used with increased frequency in paediatric practice(2). This likely reflects advances made in tertiary care of acute and chronic illnesses in infants and children, and as such is a statistic that reflects developed countries more than developing countries. The bulk of evidence-based recommendations for the use of anticoagulant therapies in children are specific for children with complex conditions requiring access to highly technical and expensive therapies(6). Table 5 presents summarises the clinical indications for anticoagulant therapy in children presented in the ACCP 2008 recommendations into 21 discrete categories(6). Of the indications within this list, only 10 indications are likely to be encountered within health services in developing countries (these have been indicated using an "**"). Of these 10 indications, consideration still needs to be given to the availability of monitoring assays to ensure the safety and efficacy of treatment provided.

Given the breadth of options available for achieving anticoagulant therapy in children even without considering novel antithrombotic agents now becoming available, clinicians face significant challenges in deciding upon the best course of treatment. Without doubt, anticoagulant therapies such as UFH and VKAs offer clinicians in developing countries significant advantages including:

i). A greater body of evidence with respect to paediatric-specific dosing and monitoring

ii). Increased affordability of both the drug and monitoring assays

Whilst these therapies certainly have the common limitation with respect to an unpredictable dose-response profile, significant literature is available to guide clinicians with respect to optimization of these therapies in children.
<table>
<thead>
<tr>
<th>Indications for Antithrombotic Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Vein Thrombosis: Central Venous Line- (CVL) and Non-Central Venous Line Related*</td>
</tr>
<tr>
<td>Veno-Occlusive Disease Prophylaxis</td>
</tr>
<tr>
<td>Neonatal Renal Vein Thrombosis*</td>
</tr>
<tr>
<td>Primary Antithrombotic Prophylaxis for CVLs</td>
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<tr>
<td>Primary Prophylaxis for Blalock-Taussig Shunts</td>
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<tr>
<td>Primary Prophylaxis for Fontan Surgery</td>
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<td>Primary Prophylaxis for Stage I Norwoods</td>
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<td>Primary Prophylaxis for Glenn or BCPS</td>
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<tr>
<td>Primary Prophylaxis for Endovascular Stents</td>
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<tr>
<td>Primary Prophylaxis for Dilated Cardiomyopathy*</td>
</tr>
<tr>
<td>Primary Pulmonary Hypertension*</td>
</tr>
<tr>
<td>Biological Prosthetic Heart Valves*</td>
</tr>
<tr>
<td>Mechanical Prosthetic Heart Valves*</td>
</tr>
<tr>
<td>Ventricular Assist Devices (VADs) and Extra-Corporeal Membranous Oxygenation (EMCO)</td>
</tr>
<tr>
<td>Therapy of Arterial Thrombosis*</td>
</tr>
<tr>
<td>Arterial Catheter Prophylaxis</td>
</tr>
<tr>
<td>Primary Prophylaxis for Venous Access related to Haemodialysis</td>
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<tr>
<td>Use of UFH or LMWH for Haemodialysis</td>
</tr>
<tr>
<td>Kawasaki Disease*</td>
</tr>
<tr>
<td>Cerebral Sinovenous Thrombosis (CSVT) and Arterial Ischaemic Stroke (AIS)*</td>
</tr>
<tr>
<td>Purpural Fulminans*</td>
</tr>
</tbody>
</table>

Table 5. Summary List of Indications for Antithrombotic Therapy in children. Adapted from(6).
References


46. Chan A, Berry L, Monagle P, Andrew M. Decreased concentrations of heparinoids are required to inhibit thrombin generation in plasma from newborns and children compared to plasma from adults due to reduced thrombin potential. Thrombosis and Haemostasis. 2002;87:606-13.


125. Chan A, Berry L, Monagle APP, Andrew M. Decreased concentrations of heparinoids are required to inhibit thrombin generation in plasma from newborns and children compared to plasma from adults due to reduced thrombin potential. Thrombosis & Haemostasis. 2002;87(4):606-13.


