PROPOSAL FOR THE INCLUSION OF LOW MOLECULAR WEIGHT HEPARINS FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED PATIENTS IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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Medicines affecting coagulation listed in the 18th EML April 2013

**Heparin sodium**
Injection: 1000 IU/mL; 5000 IU/mL; 20000 IU/mL in 1-mL ampoule

**Warfarin**
Tablet: 1 mg; 2 mg; 5 mg (sodium salt)

### 1. Summary statement of the proposal for inclusion

Venous thromboembolism (VTE) is one of the leading causes of morbidity and mortality in hospitalized patients and pulmonary embolism is responsible for 10% of overall deaths. Because symptoms of deep vein thrombosis and pulmonary embolism are non-specific, a timely diagnosis remains difficult and screening tests for VTE are not cost-effective. Thus, careful selection of patients at increased risk and application of adequate prophylactic strategies is necessary to reduce the burden of disease. There is a large amount of evidence showing the efficacy of prophylactic strategies to prevent VTE in at-risk hospitalized patients. Pharmacologic prophylaxis with either low-dose unfractionated heparin (LDUH) or low molecular weight heparin (LMWH) has been shown to reduce the risk of pulmonary embolism in general surgical patients by 75%. Because of their greater ease of use (single daily dose) and their improved safety profile (the frequency of heparin induced thrombocytopenia is three-fold lower with LMWH than with unfractionated heparin), LMWH has widely become the management of choice for prophylaxis of VTE in this setting. In patients undergoing major orthopedic surgery, LMWH has been shown to be the most effective agent before the arrival of the direct oral anticoagulant drugs (DOACs) by producing an approximately
70% risk reduction in VTE and is currently recommended as the treatment of choice in this setting (see below). It was estimated that approximately two out of three patients undergoing surgical procedures should be deemed eligible to receive antithrombotic prophylaxis. Unfortunately, the results of a large observational study carried out in several countries throughout the world (ENDORSE) reported that only about 60% of at-risk surgical patients actually receive adequate prophylactic strategies. However, this rate widely varied among countries, being highest in western European countries and lowest in low and middle income Asian countries. In countries like Bangladesh, India, Pakistan, and Thailand, prescription rates ranged between 0.2% and 16.3%. These rates were higher in Northern African countries (Egypt, Tunisia, Algeria) while no information was available for Central African countries. Insufficient availability of drugs, but also insufficient awareness of post-surgical VTE as a major clinical issue remain the main drivers for this major gap between evidences and clinical practice. For example, the incidence of post-surgical venous thrombosis has traditionally been thought to be low in Asian ethnic populations. However, recent studies have challenged this common view showing that this incidence is similar to that reported in Western countries. For these reasons, we believe that improving access to drugs with the highest effectiveness in the prevention of VTE in surgical patients has the potential to reduce the burden of disease and thrombosis related costs also in low and middle income countries. However, this improvement can only be achieved in conjunction with an improved awareness of this life-threatening disease.

2. **Name of the focal point in WHO submitting or supporting the application**

   Department of Essential Medicines and Health Products (EMP/PAU)

3. **Name of the organization consulted and supporting the application**
Scientific and Standardization Committee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis

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

Low molecular weight heparin: enoxaparin, nadroparin, dalteparin, tinzaparin, reviparin, parnaparin, certoparin, bemiparin

5. **Formulation proposed for inclusion**

Injectable, subcutaneous.

6. **International availability – sources (manufacturers and trade names)**

Enoxaparin: Clexane/Lovenox (Sanofi-Aventis Pharma), Cutenox (Gland Chemical), Dynalix (Biocon Limited), Enoxarin (Zuventus Health Care), Flothin (Ranbaxy Laboratories), Leeparin (Lee Chem Biothec Pvt), Lmwx-PFS (Nicholas Piramal India), Lovenox (Watson Pharmaceuticals), enoxaparin (Sandoz), Cardinex (Drug International), Enoparin (Popular Pharmaceuticals), Parinox (Incepta Pharma), Novex (Sothéma), Flumax (Hemolab-pharma)

Nadroparin: Fraxiparin (Aspen), Seleparina (Italfarmaco), Fraxiparine (GlaxoSmithKline), Cardioparin (Chandra Bhagat Pharma), Nadrohep (Gland Pharma), Nadroparin (Bharat Serum & Vaccines)

Dalteparin: Fragmin (P.Upjohn), Fragmin (Eisai)

Tinzaparin: Innohep (Leo Laboratories), Innohep (Ranbaxy Laboratories)

Reviparin: Clivarin (Abbott), Clivarine (Knoll), Clivarine (Abbott), Clivarina (Abbott), Lowmorin (Bayer Yakuhin)

Parnaparin: Fluxum (Alfa Wassermann), Fluxum (USV-Corvette), Lowhepa (Ajinomoto), Thromboparin (Faran Laboratories)

Certoparin: Sandoparin (Novartis), Sandoparin (Sandoz), Mono-Embolex (Novartis)
Bemiparin: Ivor (Rovi), Ivor (Sigma-Tau), Ivorat (Gineladius), Zibor (Berlin-Chemie),
Zibor (Menarini), Hibor (Biotoscana), Hibor (Dem Ilac), Hibor (Valmor), Hepadren
(Rovi), Badyket (Menarini)

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

We propose low molecular weight heparin as a pharmacological class. Although some pharmacokinetic and pharmacodynamic differences exist among different low molecular weight heparins, and although enoxaparin has the best evidence for effectiveness and safety, all low molecular weight heparins are approved for the indication discussed in this proposal and no one is consistently available with the lowest price in all considered countries.

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

VTE is a common disease and a major health problem. The annual incidence rate was estimated to be 131.5 (95% CI, 130.2-132.9) per 100,000 persons in a recent study conducted in the United Kingdom (1), 104 (95% CI 95-114) per 100,000 persons in the United States (2), and 57 (95% CI 47-67) per 100,000 persons in Australia (3). Case fatality rates at 28 days after a first lifetime VTE have been estimated to be 5% (95% CI 1-9%) after an idiopathic event, 7% (95% CI 2-13%) after a VTE provoked by trauma, surgery or immobilization, and 25% (95% CI 15-36%) in patients with cancer (4). The incidence of first-time VTE rises exponentially with age, ranging from a very low rate (0.005%/year) among children 15 years of age, to a rate of 450 to 600/100,000 per year (≈0.5%/year) among individuals over the age of 80 years (5). Ethnicity is another major determinant of VTE. Studies carried out in the United States reported a
significantly higher incidence of deep vein thrombosis and pulmonary embolism in white persons and African-Americans than in Asians and Pacific Islanders (6,7).

More than half of VTE events are related to hospitalization and are, thus, preventable (8). Surgical procedures, in particular major orthopedic surgery and cancer surgery are commonly complicated by VTE. Studies assessing the presence of asymptomatic deep vein thrombosis based on objective diagnostic screening with venography in patients not receiving prophylaxis reported incidences between 40 and 60% after hip or knee arthroplasty and between 15 and 40% after general surgery (9). The estimated rate of symptomatic VTE at approximately one month after major orthopedic surgery is 4.3% (1.5% pulmonary embolism) in patients not receiving prophylaxis and 1.8% (PE 1.55%) in patients receiving thromboprophylaxis with LMWH (10). In a large prospective study carried out in patients undergoing cancer surgery, the reported incidence of symptomatic VTE was 2.8% after abdominal surgery, with 87% of these patients receiving in-hospital prophylaxis with LMWH (11). The efficacy and safety of pharmacologic prophylaxis in surgical patients has been consistently shown by the results of several randomized controlled trials and meta-analyses and clinical guidelines recommend that all patients undergoing high-risk procedures should receive appropriate treatment (10, 12). LMWH is considered the treatment of choice for patients undergoing major orthopedic surgery, being preferred over other effective alternatives such as fondaparinux, LDUH, adjusted-dose vitamin K antagonists (VKA) or the DOACs (10). This preference is due to the favourable efficacy and safety profile, to the favourable cost-effectiveness, and to the very large experience with the use of these agents worldwide. LMWH is also recommended for high-risk surgical patients, with LDUH or fondaparinux as potential alternatives (12). LMWH is in particular proposed for patients undergoing abdominal or pelvic cancer surgery (12).
Despite clear-cut recommendations, prescription rates of adequate thromboprophylactic strategies remain below expectation. In 2008, a multinational, cross-sectional study, ENDORSE, reported the prevalence of VTE risk in the acute hospital care setting and the rates of at-risk patients who received effective prophylaxis according to recommendations from international guidelines (13). Two-thirds (64.4%) of surgical patients were defined at-risk for VTE, but only 58.5% of them received recommended VTE prophylaxis. The study was carried out in all continents and provided an interesting overview of differences among countries. What came out most strikingly from this study, albeit not surprisingly, was the very low rate of prescription of adequate prophylactic strategies documented in some countries, with the lowest rates being documented in Bangladesh (0.2%), Thailand (0.2%), Pakistan (10%), India (16%), Venezuela (23%), Russia (26%), Saudi Arabia (32%), Egypt (35%), Turkey (39%), United Arab Emirates (43%), Mexico (43%), Colombia (43%), and Brazil (46%). Reasons for these low prescription rates include lack of availability of recommended therapeutic strategies, costs of available drugs, concern about bleeding, difficulty with assessing risk level of patients, and lack of awareness of VTE as a real problem in surgical patients. This last issue possibly contributes to explain the lowest rates observed in Asian countries. Epidemiological studies from Asian countries reported VTE rates that are lower than those reported in Western countries (14-16), although a yearly increasing incidence and prevalence of venous thrombosis was consistently shown (14,16), in particular among hospitalized patients. These increasing rates suggested a possible shift in perception of the importance of the disease, a higher index of suspicion and a lower threshold for performing diagnostic tests (16), but the use of thromboprophylaxis remained extremely low. The need for such a shift is further supported by evidence from prospective observational studies.
that in Asian patients the incidence of symptomatic VTE after high risk surgery is not negligible (1.5% at one month) (17). For this reason, in the “Asia-Pacific Thrombosis Advisory Board consensus paper on prevention of venous thromboembolism after major orthopaedic surgery” it was agreed that VTE represents a threat also to Asian patients and that current international guideline recommendations for the routine use of postoperative thromboprophylaxis should be implemented in Asia. Scant information is available from other low income countries in Africa or South America, but it is highly likely that prescription rates in these countries are no better than those reported from countries participating in the ENDORSE study, thus leaving million of patients receiving surgical procedures at increased risk of pulmonary embolism and, thus, of VTE related mortality. For example, a cross-sectional study carried out in 12 hospitals in Senegal identified 60.3% surgical patients at risk for VTE, of whom 37.5% received thromboprophylaxis (18).

For this reason, the first target population for this proposal is represented by at-risk surgical patients (using definitions proposed by international guidelines) admitted to hospitals located in low and middle income countries in all continents.

9. Treatment details (dosage regimen, duration; reference to existing clinical guidelines; need for treatment monitoring facilities)

Enoxaparin 2000 IU qd (moderate risk surgical patients), 4000 IU qd (high risk surgical patients, including major orthopedic surgery in Europe), 3000 UI bid (major orthopedic surgery in the US); nadroparin 2850 IU (general surgery patients and major orthopedic surgery patients <50 kg body weight), 3800 IU qd (major orthopedic surgery patients 50-69 kg body weight), 5700 IU qd (major orthopedic surgery >70 kg); dalteparin 2500 IU (general surgery) and 5000 IU qd (major orthopedic surgery);
tinzaparin 3.500 IU qd (general surgery patients) and 50 IU/Kg qd (major orthopedic surgery); reviparin 1750 IU qd (general surgery patients) and 4.200 IU qd (major orthopedic surgery), parnaparin 3.200 IU qd (general surgery patients) and 4250 IU qd (major orthopedic surgery patients); certoparin 3000 IU qd, bemiparin 2500 IU qd (general surgery patients) and 3500 IU qd (major orthopedic surgery patients).

Recommended duration of prophylaxis varies according to surgical procedures. Extended duration pharmacologic prophylaxis is recommended for high-risk patients undergoing abdominal or pelvic surgery for cancer (4 weeks) (12) and for patients undergoing major orthopedic surgery (35 days) (10).

Platelet count monitoring is currently recommended for patients receiving heparin in whom clinicians consider the risk of heparin induced thrombocytopenia to be higher than 1% (19). For these patients, platelet count monitoring should be performed every 2 or 3 days from day 4 to day 14, or until heparin is stopped (19). Based on available evidence, the incidence of heparin induced thrombocytopenia in postoperative patients receiving LDUH ranges between 1 and 5%, in patients receiving LMWH between 0.1 and 1% (19).

Public health need and evidence appraisal and synthesis

10. Summary of comparative effectiveness (identification of clinical evidence, summary of available data, summary of available estimates of comparative effectiveness) including summary evidence tables with Grading of recommendations

LMWHs were tested against various comparators in several randomized controlled trials in different at-risk surgical populations. Taking into account that there are several differences between orthopedic and non-orthopedic surgery, especially with
regard to the risk of VTE, these two groups of surgeries are presented separately hereafter.

Non Orthopedic Surgery

- **LMWH versus no prophylaxis (Table 1)**

A meta-analysis of eight trials conducted in general and abdominal surgery showed a reduction of the risk of symptomatic VTE of about 70% (risk ratio [RR] 0.31, 95% CI 0.12-0.81) in patients who received LMWH as compared to no prophylaxis (20). Furthermore, death from any cause was possibly reduced by about 50% (RR 0.54, 95% 0.27-1.10) (20). These data have been more recently confirmed in a meta-analysis which included studies of gastrointestinal, gynecologic, urological, and thoracic surgery (21).

- **LMWH versus LDUH (Table 2)**

Results from a meta-analysis of 51 trials on more than 48,000 general and abdominal surgery patients showed that the risk of symptomatic VTE was reduced by about 30% (RR 0.71, 95% 0.51-0.99) in patients who received LMWH as compared to LDUH (20). These data have been confirmed in a more recent meta-analysis including gastrointestinal, gynecologic, urological, and thoracic patients (21).

- **LMWH versus fondaparinux**

A randomized controlled trial was conducted in patients at high risk of VTE who underwent abdominal surgery (22), comparing fondaparinux to dalteparin. The results showed that fondaparinux was non-inferior to dalteparin at reducing the composite outcome of deep vein thrombosis detected by bilateral venography and symptomatic, confirmed deep vein thrombosis or pulmonary embolism (relative risk reduction 24.6 per cent, 95% CI -9.0 to 47.9).

- **LMWH versus mechanical prophylaxis**
Data are limited to one study on trauma patients (23) and one study on gynecologic oncology patients (24). In the first trial there was no statistically significant difference in the rate of asymptomatic and symptomatic DVT between patients who received LMWH as compared to intermittent pneumatic compression (0.5% versus 2.7%, respectively, p = 0.122). In the other trial, DVT was diagnosed in 2 out of 105 patients receiving LMWH and in 1 out of 106 patients receiving external pneumatic compression, thus leading the authors to conclude for a similar effect of the tested interventions in the postoperative prophylaxis of thromboembolism.

A subgroup analysis of a recent meta-analysis (25), that included all type of mechanical compressions (pneumatic compression, foot compression and graduated compression stockings) as compared to LMWH in several groups of surgical patients, including orthopedic ones, found a significantly higher risk of DVT among patients who received mechanical compression as compared to LMWH (RR 1.80, 95% 1.16-2.79).

No trials are available for comparison of LMWH with aspirin, warfarin or new oral anticoagulants in nonorthopedic surgery.

Based on the available evidence, in 2012 the American College of Chest Physician provided an updated version of the evidence-based clinical practice guidelines for the prevention of thrombosis in nonorthopedic surgical patients (12). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the evidence and to formulate recommendations (Table 3) (26). In the context of non-orthopedic surgery, the recommendations on the use of thromboprophylaxis are based on a trade-off between the risk of VTE and the risk of major bleeding after surgery, that can be stratified according to several patient-
surgery-related variables. The risk of VTE can be considered very low (<0.5%), low (~1.5%), moderate (~3.0%) and high (~6.0%). On the other hand, the risk of major bleeding can be considered average (~1%) or high (~2%). Bleeding risk is also considered high when bleeding complications may have especially severe consequences (e.g., after craniotomy, spinal surgery, reconstructive procedures involving free flap).

Recommendations for the use of thromboprophylaxis in nonorthopedic surgery are summarized in Tables 4.

**Orthopedic Surgery**

- **LMWH versus no prophylaxis (Table 5)**

In major orthopedic surgery, that includes total hip arthroplasty (THA), total knee arthroplasty (TKA) and hip fracture surgery (HFS), the risk of symptomatic VTE was calculated from data of clinical trials enrolling more than 16,000 patients, as follows: 2.80% (PE 1.0%, DVT 1.80%) in the initial post-operative period (days 0 to 14) and 1.50% (PE 0.50%, DVT 1.00%) in the extended post-operative period (days 15-35), for a cumulative post-operative VTE incidence of 4.3% (PE 1.50%, DVT 1.80%) (10).

In the initial post-operative period, the best evidence suggests that LMWH consistently reduces DVT by about 50% after THA or TKA (combined risk ratio [RR], 0.50, 95% CI 0.43-0.59), with similar results emerging also for HFS. Combining results from all relevant studies failed to demonstrate or to exclude a beneficial effect of LMWH on PE (RR 0.58, 95% CI 0.22-1.47) (10).

In the extended post-operative period after major orthopedic surgery, LMWH was associated with a statistically significant reduction of symptomatic DVT (RR 0.46, 95%
CI 0.26-0.82), whereas a beneficial effect on PE was neither demonstrated nor excluded (RR 0.24, 95% CI 0.04-1.4)(10).

- **LMWH versus LDUH (Table 6)**

LMWH and LDUH have been compared in the initial prophylaxis after major orthopedic surgery. A subgroup analysis of a systematic review of trials comparing LMWH and UFH included 2800 patients who underwent arthroplasty or HFS (27). The results showed a 20% relative risk reduction of primarily asymptomatic DVT in favor of LMWH (RR 0.80, 95% CI 0.73-0.88) whereas they failed to demonstrate or exclude a beneficial effect of LMWH on PE (RR 0.78, 95% CI 0.49-1.24).

- **LMWH versus Vitamin K antagonists (VKAs) (Table 7-8)**

LMWH has been compared to VKAs in more than 9000 patients in several trials for the initial post-operative period after THA and TKA. The combined results showed a significantly reduced risk of symptomatic DVT associated with LMWH (RR 0.68, 95% CI 0.6-0.78), whereas they failed to establish or refute a difference in PE (RR 0.68, 95% CI 0.22-2.1)(10).

With regard to the extended prophylaxis, only one trial enrolling more than 1200 patients compared LMWH with VKA. There were no PE in the LMWH group as compared to 4 out of 636 in the VKA group. No statistically significant difference was found in the rate of asymptomatic DVT in the VKA arm as compared to LMWH arm (RR, 1.35; 95% CI, 0.70-2.6)(28).

- **LMWH versus aspirin (ASA) (Table 9)**

Evidence is limited for the head-to-head comparison between LMWH and ASA. The pooled estimate from two trials in patients undergoing THA or TKA showed a higher incidence of asymptomatic DVT associated with aspirin compared to LMWH (RR 1.87,
95% CI 1.3-2.7), whereas PE were too few to provide an accurate estimate and no major bleeding events were reported (10,29,30)

- **LMWH versus fondaparinux (Table 10)**

Several large trials compared fondaparinux with LMWH for the initial VTE prophylaxis after major orthopedic surgery. The pooled results failed to demonstrate or exclude a beneficial effect of fondaparinux on symptomatic DVT (RR 1.31, 0.47-3.7) and PE (RR 1.32, 0.37-4.74) (10).

- **LMWH versus new oral anticoagulants (Table 11)**

Several trials have been conducted more recently to compare a new generation of oral anticoagulant drugs (two direct factor-Xa inhibitors, rivaroxaban and apixaban, and one direct thrombin inhibitor, dabigatran) with LMWH after TKA or THA.

More than 10000 patients were enrolled in randomized controlled trials (RCTs) comparing rivaroxaban with LMWH. The pooled results showed a statistically significant reduction in symptomatic DVT in rivaroxaban arms (RR 0.41, 95% CI 0.2-0.83), whereas they failed to demonstrate or exclude a beneficial effect of rivaroxaban on PE (RR 1.34, 95% CI 0.39-4.6) (10).

Four RCTs compared dabigatran with LMWH in patients undergoing THA or TKA, enrolling more than 10000 patients. The pooled estimates failed to demonstrate or exclude a difference in the number of symptomatic VTEs for both dabigatran dose regimens of 220 mg (PE: RR 1.22, 95% CI 0.52-2.85; DVT: RR 0.7, 95% CI 0.12-3.91) and 150 mg (PE: RR 0.31, 95% CI 0.04-2.48; DVT: RR 1.52, 95% CI 0.45-5.05), as compared to LMWH (10).

Finally, apixaban was compared to LMWH in four RCTs enrolling more than 12000 patients undergoing THA or TKA. The pooled analysis found that apixaban significantly reduced symptomatic DVT by 59% (RR 0.41, 95% CI 0.18-0.95), but failed to
demonstrate a beneficial or detrimental effect on nonfatal PE (RR 1.09, 95% CI 0.31-3.88) (10).

- **LMWH versus mechanical prophylaxis (Table 12)**

Pneumatic compression devices (i.e. intermittent pneumatic compression device and venous foot pump) were compared with LMWH in more than 1000 patients undergoing THA and TKA. Overall, there was a trend associated with compression devices toward an increase in asymptomatic DVT (RR 1.38, 95% CI 0.92-2.06) and in nonfatal PE (RR 2.92, 0.12-71), even if not statistically significant (10).

Based on the available evidence, in 2012 the American College of Chest Physician provided an updated version of the evidence-based clinical practice guidelines for the prevention of thrombosis in orthopedic surgical patients (10). Similarly to the methodology used for non-orthopedic surgery, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the evidence and to formulate the recommendations (Table 3)(26).

In the context of orthopedic surgery, the recommendations on the use of thromboprophylaxis are based on a trade-off between the risk of VTE and the risk of major bleeding after surgery. For major orthopedic surgery, differently from non-orthopedic surgery, the surgery-specific risk of VTE far outweighs the contribution of the patient-specific factors. Indeed, no individual risk estimation was sufficiently secure in this clinical context to mandate different recommendations for different risk strata. Therefore, recommendations for the prevention of VTE in orthopedic surgery (summarized in Table 13) are not based on an individual stratification of the risk of VTE and bleeding.
11. Summary of comparative evidence on safety (description of adverse effects/reactions; identification of variation in safety due to health systems and patient factors; summary of comparative safety against comparators) including summary evidence tables with Grading of recommendations

The evaluation of safety related to LMWH includes hemorrhagic and nonhemorrhagic complications.

**Hemorrhagic complications**

With regard to the risk of bleeding associated with the use of thromboprophylaxis after surgical intervention, a distinction between orthopedic and non-orthopedic surgery is made and the two groups of surgery are presented separately hereafter.

**Non Orthopedic surgery**

- *LMWH versus no prophylaxis (Table 14)*

A meta-analysis of eight trials conducted in general and abdominal surgery showed an approximate doubling of the risk of major bleeding (RR 2.03, 95% CI 1.37-3.01) and wound hematoma (RR 1.88, 95% CI 1.54-2.28) associated with LMWH, as compared to no prophylaxis (20). These data have been more recently confirmed in a meta-analysis which included studies of gastrointestinal, gynecologic, urological, and thoracic surgery (21).

- *LMWH versus LDUH (Table 14)*

Results from a meta-analysis of 51 trials on more than 48000 general and abdominal surgery patients failed to demonstrate or to exclude a beneficial effect of LMWH as compared to LDUH on major bleeding and wound hematoma (RR 0.89, 95% CI 0.75-1.05) (20). These data have been confirmed in a more recent meta-analysis including gastrointestinal, gynecologic, urological, and thoracic patients (21).
- **LMWH versus fondaparinux**

A randomized controlled trial compared fondaparinux to dalteparin in patients at high risk of VTE who underwent abdominal surgery (22). The results showed a possible increase in the risk of nonfatal major bleeding with fondaparinux (RR 1.43, 95% CI 0.93-2.21), but differences in the risks of fatal bleeding and bleeding requiring reoperation were neither confirmed nor excluded.

- **LMWH versus mechanical prophylaxis**

Specific data for this comparison are limited to one study on trauma patients (23) and one study on gynecologic oncology patients (24). In the first trial there was no statistically significant difference in the rate of major bleeding between patients who received LMWH as compared to intermittent pneumatic compression (4 in each group). In the other trial, the frequency of bleeding complications, measured by the number of required perioperative transfusions, and estimated intraoperative blood loss was similar between the two groups.

A subgroup analysis of a recent meta-analysis (25, 28), that compared all types of mechanical compression (pneumatic compression, foot compression and graduated compression stockings) to LMWH in several groups of surgical patients, including orthopedic ones, found a statistically significant reduction in the risk of major bleeding with compression devices as compared to LMWH (RR 0.51, 95% CI 0.40, 0.64)

- **No trials are available for comparison of LMWH with aspirin, warfarin or new oral anticoagulants.**

**Orthopedic surgery** (Table 15)

- **LMWH versus no prophylaxis**
In major orthopedic surgery, the baseline risk of major bleeding was estimated for the initial post-operative period (days 0 to 14) from the placebo arm of LMWH trials, resulting in a median rate of 1.5% (10). This estimate is consistent with that found in a systematic review, ranging from 1% to 2% (27). The expected risk of major bleeding with LMWH has been shown to be very close to that of placebo, with a large CI (RR 0.81, 95% CI 0.38-1.72) (10,31).

Similarly, in the extended post-operative period (days 15 to 35), results from a meta-analysis failed to demonstrate or exclude an effect of LMWH on major bleeding (RR 0.43, 95% CI 0.11-1.65) (10).

- **LMWH versus LDUH**

LMWH and LDUH have been compared in the initial prophylaxis after major orthopedic surgery. A subgroup analysis of a systematic review of trials comparing LMWH and UFH included 2800 patients who underwent arthroplasty or HFS (27). The pooled analysis failed to demonstrate or exclude a beneficial effect of LMWH as compared to UFH (RR 0.91, 95% CI 0.75-1.09).

- **LMWH versus VKAs**

LMWH has been compared to VKAs in more than 9000 patients in several trials for the initial post-operative period after THA and TKA. The combined results showed no significant difference in major bleeding events (RR 1.36, 95% CI 0.95-1.96).

With regard to the extended prophylaxis, only one trial enrolling more than 1200 patients compared LMWH with VKA. A substantial increase in major bleeding was found with VKAs(RR 3.9, 95 % CI 1.9-8.1)(10).

- **LMWH versus aspirin (ASA)**
Evidence is limited for the head-to-head comparison between LMWH and ASA. In the two trials in patients undergoing THA or TKA no major bleeding events were reported in both arms (29, 30).

- LMWH versus fondaparinux

Several large trials compared fondaparinux with LMWH for the initial VTE prophylaxis after major orthopedic surgery. The pooled results show a significant increase in bleeding requiring re-operation associated with fondaparinux (RR 1.85, 95% CI 1.1-3.11), even if there was not a statistically significant difference in the rate of major bleeding (RR 1.35, 95% CI 0.89-2.05) (10).

- LMWH versus new oral anticoagulants

Several trials have been recently conducted to compare a new generation of oral anticogulant drugs (two direct factor-Xa inhibitors, rivaroxaban and apixaban, and one direct thrombin inhibitor, dabigatran) with LMWH after TKA or THA.

With regard to rivaroxaban, in a pooled analysis of seven trials enrolling more than 10000 patients, there was a trend toward increased major bleeding and bleeding requiring reoperation, although not statistically significant (major bleeding: RR 1.58 95% CI, 0.84-2.97; bleeding requiring reoperation: RR 2.0 95% CI 0.86-4.83; combined: RR 1.73, 95% CI, 0.94-3.17) (10).

Four RCTs compared dabigatran with LMWH in patients undergoing THA or TKA, enrolling more than 10000 patients. The pooled estimates failed to demonstrate or exclude a difference in the number of major bleeding events for both dabigatran dosage regimens of 220 mg (RR 1.06, 95% CI, 0.66-1.72) and 150 mg (RR 0.71, 95% CI 0.42-1.19) (10).
Finally, apixaban was compared to LMWH in four RCTs enrolling more than 12000 patients undergoing THA or TKA. The pooled analysis failed to demonstrate or exclude a difference in the number of major bleeding (RR 0.76, 95% CI 0.44-1.32) (10).

- LMWH versus mechanical prophylaxis

Pneumatic compression devices (i.e. intermittent pneumatic compression device and venous foot pump) were compared with LMWH in more than 1000 patients undergoing THA and TKA. The pooled analysis showed a statistically significant reduction of the risk of major bleeding associated with compression devices (RR, 0.32, 95% CI 0.12-0.89) (10).

Non-hemorrhagic complications

*Heparin induced thrombocytopenia (HIT).* This potentially severe complication is represented by a fall in platelet count after exposure to heparin and an associated prothrombotic syndrome. Indeed, heparin-dependent IgG antibodies bind to multimolecular complexes consisting of platelet factor 4 bound to heparin, thus causing platelets activation (with release of highly prothrombotic microparticles) and their removal from the circulation (with consequent thrombocytopenia).

Several factors influence the incidence of HIT, including the type and preparation of heparin (UFH or LMWH) and the heparin-exposed patient population, with the postoperative patients presenting a higher risk.

A recent Cochrane systematic review and meta-analysis specifically compared the incidence of HIT after exposure to UFH or LMWH after any surgical intervention. The results show a statistically significant reduction in the risk of HIT with LMWH as compared to UFH (risk ratio 0.24, 95% CI 0.07-0.82) (32).
Osteoporosis. In addition to its anticoagulant effects, heparin binds to a number of proteins and cells, including osteoblasts, which then release factors that activate osteoclasts and promote bone loss. Compared to UFH, LWMH has lower affinity for proteins and cells, resulting also in a decreased binding to osteoblasts. Long-term use of UFH has been associated with a 2.2–5% incidence of heparin-induced osteoporotic fracture, but accurate data for LMWH data are scarce. Indeed, a recent systematic review identified only 9 cases of LMWH-induced osteoporosis from 13 articles (33). With regard to the comparison of the risk of osteoporosis between heparins, only two small trials have been conducted, both in pregnant women who have been assigned to receive prophylactic doses of UFH or LMWH during pregnancy. In the first trial, mean bone density of the lumbar spine was significantly lower in the UFH group than in the LWMH group. Moreover, bone density measurements did not differ between the LMWH group and a control group of healthy untreated women (34). In the second trial, one out of 49 women (2.3%) in the LMWH group had significant bone loss at the total proximal femur (defined as a decrease of >10%), compared with none of the 40 patients in the UFH group (35). The authors of the abovementioned systematic review conclude that, until large clinical trials are designed to investigate pre- and post-treatment bone density and to compare different dosages of LMWH effect on the bone density in different patient groups, no accurate conclusions can be made on the risk of osteoporosis related to LMWH.

12. Summary of available data on comparative costs and cost-effectiveness within the pharmacological class or therapeutic group (range of costs of the proposed medicine; comparative cost-effectiveness presented as range of cost per routine outcome)
Collecting data from different counties including Algeria, Argentina, Brazil, India, Morocco, Thailand, Tunisia, and Uganda, the costs of prophylactic doses of LMWH ranged from 2.25 to 9.5 USD per dose for the 20 mg prophylactic dose of enoxaparin (20 mg) to 4.75 to 18.5 USD per dose for the 40 mg prophylactic dose of enoxaparin, that is the most widely used LMWH across countries. Biosimilar LMWH can be found at lower costs, where available. Studies assessing the cost-effectiveness of VTE prophylaxis in hospitalized patients have been carried out in Western countries. The use of pharmacologic prophylaxis was recently confirmed to be associated with substantial cost savings in studies from Australia, Europe and North America (36-38). The total cost of prophylaxis with LMWH was lower than the cost with UFH in a population of high risk medical patients (39). No cost-effectiveness studies of VTE prophylaxis are available from developing countries. However, cost-effectiveness studies comparing LMWH and UFH for the treatment of acute VTE from China and Brazil found lower costs with the former than with the latter (40,41).

**Regulatory information**

13. **Summary of regulatory status of the medicine (different countries)**

In all countries, LMWH is approved for the prevention of VTE in surgical patients with moderate or high risk for VTE; for the prevention of VTE in medical patients with congestive heart failure (NYHA class III or IV), respiratory failure, acute infection or acute rheumatologic disease with at least one risk factor for VTE; for the prevention of blood clot in the extra-corporeal circulation during hemodialysis; for treatment of DVT with or without PE; for the treatment of unstable angina and non-Q-wave AMI (in conjunction with aspirin); for the treatment of AMI with ST-segment elevation. Indications may vary across LMWHs.
14. **Availability of pharmacopoeial standards**

British Pharmacopoeia: Yes

International Pharmacopoeia: Yes

United States Pharmacopoeia: Yes

European Pharmacopoeia: Yes

15. **Proposed text for the WHO Model Formulary**

Based on current evidence, medicines in the following two classes of parenteral anticoagulants (UFH and LWMH) are included as essential medicines for the prevention of venous thromboembolism in hospitalized patients undergoing high risk surgical procedures (e.g. cancer surgery and major orthopedic surgery). WHO recommends and endorses the local implementation of protocols for VTE prevention and emphasizes the importance of using these products in accordance with international and national guidelines. LMWH have advantages over UFH and should be preferred where available.
References


28) Samama CM, Vray M, Barré J, et al; SACRE Study Investigators. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-
2002;162(19):2191-2196


30) Graor RASJ, Lotke PA, Davidson BL. RD heparin (arde-parin sodium) vs. aspirin to prevent deep venous thrombosis after hip or knee replacement surgery [abstract]. Chest. 1992;102(suppl):118S.


40) Chen L, Ying K, Hong W, Zhou P. Comparison of low molecular weight heparin and unfractionated heparin for acute PTE. J Zhejiang Univ Science B 2005;6:1195-1199

### Table 1. Risk of VTE in non-orthopedic surgery: LMWH versus no prophylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline risk</th>
<th>Risk LMWH (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>3 per 1000</td>
<td>2 per 1000 (1-3)</td>
<td>RR 0.54 (0.27-1.1)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>6 per 1000</td>
<td>3 per 1000 (2-7)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>12 per 1000</td>
<td>6 per 1000 (3-13)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic VTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>15 per 1000</td>
<td>5 per 1000 (2-12)</td>
<td>RR 0.31 (0.12-0.81)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>30 per 1000</td>
<td>9 per 1000 (4-24)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>60 per 1000</td>
<td>19 per 1000 (7-49)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Risk of VTE in non-orthopedic surgery: LMWH versus LDUH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LDUH</th>
<th>Risk LMWH (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>3 per 1000</td>
<td>3 per 1000 (1-3)</td>
<td>RR 1.04 (0.89-1.2)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>6 per 1000</td>
<td>6 per 1000 (2-7)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>12 per 1000</td>
<td>12 per 1000 (3-13)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic VTE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>7 per 1000</td>
<td>5 per 1000 (4-7)</td>
<td>RR 0.71 (0.51-0.99)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>13 per 1000</td>
<td>9 per 1000 (7-13)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>26 per 1000</td>
<td>18 per 1000 (13-26)</td>
<td></td>
</tr>
<tr>
<td>Grade of Recommendation</td>
<td>Benefit vs Risk and Burdens</td>
<td>Methodologic Strength of Supporting Evidence</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Strong recommendation, high-quality evidence (1A)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies</td>
<td></td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies</td>
<td></td>
</tr>
<tr>
<td>Strong recommendation, low- or very-low-quality evidence (1C)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence</td>
<td></td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies</td>
<td></td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies</td>
<td></td>
</tr>
<tr>
<td>Weak recommendation, low- or very-low-quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Recommendations for thromboprophylaxis in various risk groups in non orthopedic surgery

<table>
<thead>
<tr>
<th>Risk of symptomatic VTE</th>
<th>Average risk (~1%)</th>
<th>High risk (~2%) or severe complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (&lt; 0.5%)</td>
<td>No specific prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Low (~1.5%)</td>
<td>Mechanical prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Moderate (~3%)</td>
<td>LMWH (Grade 2B) or LDUH (Grade 2B) or Mechanical prophylaxis (Grade 2C)</td>
<td>Mechanical prophylaxis (Grade 2C)</td>
</tr>
<tr>
<td>High (~6%)</td>
<td>LMWH (Grade 1B) or LDUH (Grade 1B) plus Mechanical prophylaxis (Grade 2C)</td>
<td>Mechanical prophylaxis until risk of bleeding diminishes and pharmacologic prophylaxis can be added (Grade 2C)</td>
</tr>
</tbody>
</table>

Table 5. Risk of VTE in major orthopedic surgery: LMWH versus no prophylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline risk</th>
<th>Risk difference with LMWH (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td></td>
<td>Initial prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(from 8 fewer to 5 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extended prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(from 5 fewer to 2 more)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td></td>
<td>Initial prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 per 1000</td>
<td>9 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(from 7 fewer to 10 fewer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extended prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 per 1000</td>
<td>5 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(from 2 fewer to 7 fewer)</td>
</tr>
</tbody>
</table>

Table 6. Risk of VTE in major orthopedic surgery: LMWH versus LDUH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LDUH</th>
<th>Risk difference with LMWH (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>Initial prophylaxis</td>
<td></td>
<td>0.78 (0.49-1.24)</td>
</tr>
<tr>
<td></td>
<td>4 per 1000</td>
<td>1 fewer per 1000</td>
<td>(from 2 fewer to 1 more)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>Initial prophylaxis</td>
<td></td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td></td>
<td>12 per 1000</td>
<td>2 fewer per 1000</td>
<td>(from 2 fewer to 3 fewer)</td>
</tr>
</tbody>
</table>
### Table 7. Risk of VTE in major orthopedic surgery: LMWH versus VKAs - initial prophylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk VKAs</th>
<th>Risk difference with LMWH (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td>Initial prophylaxis</td>
<td>2 per 1000 to 1 fewer per 1000 (from 2 fewer to 3 more)</td>
<td>0.68 (0.22-2.1)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>Initial prophylaxis</td>
<td>5 per 1000 to 2 fewer per 1000 (from 1 fewer to 2 fewer)</td>
<td>0.68 (0.6-0.78)</td>
</tr>
</tbody>
</table>

### Table 8. Risk of VTE in major orthopedic surgery: VKAs versus LMWH - extended prophylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LMWH</th>
<th>Risk difference with VKAs (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td>Extended prophylaxis</td>
<td>6 per 1000 to 45 more per 1000 (from 5 fewer to 96 more)</td>
<td>9.1 (0.49-169)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>Extended prophylaxis</td>
<td>12 per 1000 to 4 fewer per 1000 (from 4 fewer to 20 more)</td>
<td>1.35 (0.7-2.6)</td>
</tr>
</tbody>
</table>

### Table 9. Risk of VTE in major orthopedic surgery: ASA versus LMWH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LMWH</th>
<th>Risk difference with ASA (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic DVT</td>
<td>Full 35-day prophylaxis</td>
<td>12 per 1000 to 11 more per 1000 (from 4 more to 21 more)</td>
<td>1.87 (1.3-2.7)</td>
</tr>
</tbody>
</table>

### Table 10. Risk of VTE in major orthopedic surgery: fondaparinux versus LMWH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LMWH</th>
<th>Risk difference with fondaparinux (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td>Initial prophylaxis</td>
<td>4 per 1000 to 1 more per 1000 (from 2 fewer to 13 more)</td>
<td>1.32 (0.37-4.74)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>Initial prophylaxis</td>
<td>8 per 1000 to 2 more per 1000 (from 4 fewer to 22 more)</td>
<td>1.31 (0.47-3.7)</td>
</tr>
</tbody>
</table>
Table 11. Risk of VTE in major orthopedic surgery: new oral anticoagulants versus LMWH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LMWH</th>
<th>Risk difference with rivaroxaban (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td></td>
<td>Full 35-d prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 per 1000</td>
<td>2 more per 1000</td>
<td>1.34 (0.39-4.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 3 fewer to 20 more)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 per 1000</td>
<td>1 more per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 3 fewer to 10 more)</td>
<td></td>
</tr>
<tr>
<td>Risk LMWH</td>
<td></td>
<td>6 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 5 fewer to 8 more)</td>
<td></td>
</tr>
<tr>
<td>Risk LMWH</td>
<td></td>
<td>6 per 1000</td>
<td>0 more per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 4 fewer to 16 more)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Risk LMWH</td>
<td>Full 35-d prophylaxis</td>
<td>0.41 (0.2-0.83)</td>
</tr>
<tr>
<td>DVT</td>
<td>12 per 1000</td>
<td>7 fewer per 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 2 fewer to 10 fewer)</td>
<td></td>
</tr>
<tr>
<td>Risk LMWH</td>
<td></td>
<td>12 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 11 fewer to 36 more)</td>
<td></td>
</tr>
<tr>
<td>Risk LMWH</td>
<td></td>
<td>12 per 1000</td>
<td>6 more per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 7 fewer to 51 more)</td>
<td></td>
</tr>
<tr>
<td>Risk LMWH</td>
<td></td>
<td>12 per 1000</td>
<td>7 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from 1 fewer to 10 fewer)</td>
<td></td>
</tr>
</tbody>
</table>
Table 12. Risk of VTE in major orthopedic surgery: mechanical compression versus LMWH

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk LMWH</th>
<th>Risk difference with compression devices (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal PE</td>
<td>Initial prophylaxis</td>
<td>4 per 1000</td>
<td>7 more per 1000 (from 3 fewer to 80 more)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>Initial prophylaxis</td>
<td>8 per 1000</td>
<td>3 more per 1000 (from 1 fewer to 8 more)</td>
</tr>
</tbody>
</table>

Table 13. Recommendations for thromboprophylaxis in orthopedic surgery

<table>
<thead>
<tr>
<th>THA</th>
<th>TKA</th>
<th>HFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial prophylaxis (minimum of 10 to 14 days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THA</td>
<td>TKA</td>
<td>HFS</td>
</tr>
<tr>
<td>LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban,</td>
<td>LMWH, fondaparinux, LDUH,</td>
<td></td>
</tr>
<tr>
<td>LDUH, VKA, aspirin (all Grade 1B)</td>
<td>VKA, aspirin (all Grade 2B)</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>ICPD (Grade 1C)</td>
<td>IPCD (Grade 1C)</td>
<td></td>
</tr>
<tr>
<td><strong>Extended prophylaxis (up to 35 days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suggestion to extend thromboprophylaxis up to 35 days (Grade 2B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Irrespective of length of treatment or concomitant IPCD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH in preference to fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), VKA, aspirin (all grade 2C)</td>
<td>LMWH in preference to fondaparinux, LDUH (all Grade 2B), VKA, aspirin (all grade 2C)</td>
<td></td>
</tr>
</tbody>
</table>

Table 14. Risk of major bleeding in non orthopedic surgery

<table>
<thead>
<tr>
<th>Risk of major bleeding (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>RR 2.03 (1.37-3.01)</td>
</tr>
<tr>
<td>Low risk population</td>
<td></td>
</tr>
<tr>
<td>12 per 1000</td>
<td>24 per 1000 (16-36)</td>
</tr>
<tr>
<td>Medium risk population</td>
<td></td>
</tr>
<tr>
<td>22 per 1000</td>
<td>45 per 1000 (30-66)</td>
</tr>
<tr>
<td>LDUH</td>
<td>RR 0.89 (0.75-1.05)</td>
</tr>
<tr>
<td>Low risk population</td>
<td></td>
</tr>
<tr>
<td>19 per 1000</td>
<td>17 per 1000 (14-20)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td></td>
</tr>
<tr>
<td>35 per 1000</td>
<td>31 per 1000 (26-37)</td>
</tr>
</tbody>
</table>
### Table 15. Risk of major bleeding in major orthopedic surgery

<table>
<thead>
<tr>
<th>Risk of major bleeding (95% CI)</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Initial prophylaxis</td>
<td>0.81 (0.38-1.72)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>3 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 9 fewer to 11 more)</td>
</tr>
<tr>
<td>Extended prophylaxis</td>
<td>0.43 (0.11-1.65)</td>
</tr>
<tr>
<td>5 per 1000</td>
<td>3 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 4 fewer to 3 more)</td>
</tr>
<tr>
<td><strong>Risk LDUH</strong></td>
<td></td>
</tr>
<tr>
<td>Initial prophylaxis</td>
<td>0.91 (0.75-1.09)</td>
</tr>
<tr>
<td>16 per 1000</td>
<td>1 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 4 fewer to 1 more)</td>
</tr>
<tr>
<td><strong>Risk VKAs</strong></td>
<td></td>
</tr>
<tr>
<td>Initial prophylaxis</td>
<td>1.36 (0.95-1.96)</td>
</tr>
<tr>
<td>11 per 1000</td>
<td>4 more per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 1 fewer to 11 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Extended prophylaxis</td>
<td>3.93 (1.91-8.11)</td>
</tr>
<tr>
<td>14 per 1000</td>
<td>41 more per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 13 more to 100 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Initial prophylaxis</td>
<td>1.35 (0.89-2.05)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>5 more per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 2 fewer to 16 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Full 35-day prophylaxis</td>
<td>1.58 (0.84-2.97)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>9 more per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 2 fewer to 30 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Full 35-day prophylaxis</td>
<td>1.06 (0.66-1.72)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>1 more per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 5 fewer to 11 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Full 35-day prophylaxis</td>
<td>0.71 (0.42-1.19)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 9 fewer to 3 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Full 35-day prophylaxis</td>
<td>0.76 (0.44-1.32)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>4 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 8 fewer to 5 more)</td>
</tr>
<tr>
<td><strong>Risk LMWH</strong></td>
<td></td>
</tr>
<tr>
<td>Initial prophylaxis</td>
<td>0.32 (0.12-0.89)</td>
</tr>
<tr>
<td>15 per 1000</td>
<td>10 fewer per 1000</td>
</tr>
<tr>
<td></td>
<td>(from 2 fewer to 13 fewer)</td>
</tr>
</tbody>
</table>