Pharmacological Venous Thromboembolism Prophylaxis in Hospitalized Medical Patients

A Meta-analysis of Randomized Controlled Trials

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Background: There is uncertainty regarding which pharmacological agents most effectively prevent venous thromboembolism in hospitalized medical patients. We therefore performed a meta-analysis to determine this.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1950, 1966, and 1800, respectively, through June 30, 2006, for randomized controlled trials that involved medical patients comparing unfractionated heparin (UFH) or low-molecular-weight heparin or heparinoid (LMWH) with a control, LMWH with UFH, or selective factor Xa inhibitors with a comparator. Study selection, validity assessment, and data abstraction were performed by 2 independent reviewers (L.W. and S.W.). Data synthesis was undertaken by 1 blinded investigator (S.J.H.).

Results: Thirty-six studies were included. Compared with the control, UFH was associated with a reduced risk of deep venous thrombosis (DVT) (risk ratio [RR], 0.33; 95% confidence interval [CI], 0.26-0.42) and pulmonary embolism (RR, 0.64; 95% CI, 0.50-0.82), as was LMWH (RR, 0.56; 95% CI, 0.45-0.70; and RR, 0.37; 95% CI, 0.21-0.64, respectively). A UFH dosage of 5000 U 3 times daily was more effective in preventing DVT than a UFH dosage of 5000 U twice daily when compared with the control (RR, 0.27; 95% CI, 0.20-0.36; vs RR, 0.52; 95% CI, 0.28-0.96). Neither UFH nor LMWH reduced mortality. When directly compared with UFH, LMWH was associated with a lower risk of DVT (RR, 0.68; 95% CI, 0.52-0.88) and injection site hematoma (RR, 0.47; 95% CI, 0.36-0.62), but no difference was seen between the 2 agents in the risk of bleeding or thrombocytopenia.

Conclusions: Both UFH and LMWH reduce venous thromboembolic risk in hospitalized medical patients, but neither agent alters mortality. When directly compared, LMWH is more effective in preventing DVT.

Arch Intern Med. 2007;167(14):1476-1486

VENOUS THROMBOEMBOLISM (VTE), which consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major and often unrecognized cause of morbidity and mortality in hospitalized patients.1-3 Approximately 10% of hospital deaths can be attributed to pulmonary emboli.4-6 It is widely accepted that reliance on the diagnosis and treatment of an established event is an inappropriate way to approach VTE because diagnosis is often difficult and massive PE may be the first clinical manifestation of the disease.7-11 Prevention is therefore of paramount importance.

Thromboprophylaxis is routinely used in surgical patients. However, it is not as widely practiced in the medical setting, even though medical patients represent most hospitalized patients and at least 75% of fatal PEs occur in this group.12 Unfractionated heparin (UFH), low-molecular-weight heparin or heparinoid (LMWH), and selective factor Xa inhibitors are all used for the prevention of VTE. Current International Consensus Statement11 and American College of Chest Physicians17 guidelines recommend the use of UFH or LMWH in medical patients at risk for VTE. We performed a meta-analysis of randomized controlled trials to compare the efficacy and safety of the various agents available for thromboprophylaxis.

METHODS

STUDY SEARCH

MEDLINE (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1950, 1966, and 1800, respectively, through June 30, 2006. MEDLINE
and the Cochrane Central Register of Controlled Trials were searched using the medical subject heading terms heparin, venous thrombosis, and pulmonary embolism. EMBASE was searched using the EMTREE keywords heparin and venous thromboembolism. These databases were also searched using the term factor Xa inhibitor. All searches were restricted to trials that involved humans and were published in English. In addition, the reference lists of all relevant trials were hand searched.

STUDY SELECTION, VALIDITY ASSESSMENT, AND DATA ABSTRACTION

Only prospective randomized controlled trials were considered for inclusion in this meta-analysis. Studies were eligible if they compared (1) UFH with the control, (2) LMWH with the control, (3) LMWH with UFH, or (4) a selective factor Xa inhibitor with a placebo. Studies were considered appropriate for inclusion only if they involved hospitalized medical patients and reported the occurrence of DVT, PE, and/or mortality after the administration of therapy.

Studies with fewer than 30 patients were excluded. Studies were also excluded if they examined thromboembolism in surgical, trauma, or critical care patients only or if the study authors did not provide a subgroup analysis for medical patients regarding the occurrence of thromboembolism. In addition, trials that studied thromboembolism associated with central venous catheters in patients with cancer and trials that involved patients admitted to intensive care units were excluded.

Study selection, validity assessment, and data abstraction were performed by 2 independent reviewers (L.W. and S.W.) in an unblinded standardized manner. Two other investigators (H.K. and J.S.) were consulted whenever the need arose for further discussion about the eligibility of a trial for inclusion in this meta-analysis or about results reported by individual studies. This process was undertaken in accordance with the guidelines of the Quality of Reporting of Meta-analyses statement.18

OUTCOME MEASURES AND APPLIED DEFINITIONS

We were able to conduct a meta-analysis for a particular outcome if it was investigated in 3 or more trials. DVT, PE, mortality, and total bleeding were analyzed in studies that compared LMWH with the control, UFH with the control, and LMWH with UFH. Results of all studies that compared UFH, LMWH, or factor Xa inhibitor with the control were combined to produce an analysis of prophylaxis vs no prophylaxis for these outcomes. Studies that compared LMWH with the control and LMWH with UFH had also provided further details regarding other outcome measures, which have been analyzed in this investigation: major bleeding, minor bleeding, thrombocytopenia, and injection site hematomas. In addition, UFH dosages of 3000 U twice daily and 5000 U 3 times daily were analyzed separately by comparison with the control for the outcome of DVT.

The definitions of outcome measures were considered to be those provided by the authors of the various studies with the exception of total bleeding and major bleeding. Intracerebral and intracranial hemorrhages and hemorrhagic transformations were included in the definition of total bleeding and major bleeding episodes. The outcome of total bleeding includes major, minor, and fatal bleeding episodes but not subcutaneous injection site hematomas.

The raw data results reported by the authors of the studies were used in this meta-analysis. Where the required values were not explicitly and unambiguously reported by the authors, the number of participants in the study was assumed to be the number who started treatment for all outcomes analyzed, except for DVT. In the case of DVT, the total number of patients was deemed to be the number who completed the trial as set out in the individual study protocols for that outcome. The reason for this discrepancy is that in some of the trials, several randomized patients did not undergo assessment for DVT. Therefore, the proportion of patients who underwent investigation who were found to have DVT would more closely reflect the true rate of DVT than the proportion of all patients who started treatment.

QUANTITATIVE DATA SYNTHESIS

Formal quantitative data synthesis was undertaken in a blinded manner by 1 investigator (S.J.H.) in consultation with 2 other investigators (L.W. and S.W.). Data analysis was conducted with STATA statistical software, version 8.2 (StataCorp, College Station, Texas) using the Mantel-Haenszel fixed-effect method and the DerSimonian and Laird random-effects method in meta-analysis for binary outcomes. The fixed-effects model calculates an average of the outcome statistic from each study, whereas the random-effects model additionally considers the variability among the studies analyzed. Results were presented as estimates of relative risk (RR) for each outcome measure, with 95% confidence intervals (CIs), in which relative weights were assigned to each study on the basis of treatment group size and number of observed events. Heterogeneity χ2 tests were performed in each analysis, and statistical significance was assumed at the .05 level via the use of statistical 2-way χ2 tests. Sensitivity analyses were performed to assess the impact of each individual trial on the final pooled estimate for each outcome measure. Funnel plots were constructed via RevMan Analyses, version 1.0.5 (the Nordic Cochrane Centre, Copenhagen, Denmark) to investigate the potential for publication bias.

RESULTS

SEARCH RESULTS

Our search for studies conducted in accordance with the Quality of Reporting of Meta-analyses statement19 is summarized in Figure 1. We identified 936 potentially suitable articles. Of these, 54 examined the relevant end points in appropriate patient groups. Nine of these trials21-29 were excluded because they did not compare (1) UFH with the control, (2) LMWH with the control, (3) LMWH with UFH, or (4) a selective factor Xa inhibitor with a comparator. Four studies30-33 were excluded because they were not randomized controlled trials, and 2 studies34,35 were excluded because of potential biases from the study randomization process. One article36 was excluded because it was an abstract that outlined research later published in another journal.37 One additional study38 was excluded because it was not possible to extract sufficient data from the published article for statistical analysis to be performed (the number of patients in each group who experienced an event and the number of patients randomized to each group were required). The remaining 36 trials39-72 were included in this meta-analysis (Table 1).

STUDY CHARACTERISTICS

Among the 36 trials included in this meta-analysis, 4 different comparisons of therapy were studied. Fourteen trials compared UFH with the control,40-63 11 trials compared LMWH with the control,39,49-50 10 compared LMWH
Several different modes of investigation were used to diagnose DVT among the trials. Venography, iodine 125 fibrinogen scanning, impedance plethysmography, and ultrasonography were all used. Alternatively, in some cases DVT was diagnosed either clinically or at autopsy. In one study, the method used to diagnose reported DVT was not specified.

Methods used to diagnose PE were ventilation and perfusion lung scanning, pulmonary angiography, spiral computed tomography, and chest radiography. In some studies, PE was diagnosed clinically or at autopsy. The method used was not specified in some studies, whereas in others described the number of events or episodes observed. When possible, we used data for the number of patients who experienced the relevant outcomes. Furthermore, in their results sections, some authors did not provide data for the total number of patients who experienced bleeding yet reported subcategories of this outcome separately. When this occurred, we added the patients or episodes into the different subcategories to obtain a combined figure for the purposes of our analysis of total bleeding. Major and minor bleeding episodes were also occasionally reported in terms of subcategories.

**QUANTITATIVE FINDINGS**

Unless otherwise stated, reported figures are discussed in the context of the fixed-effects mode because of no major apparent difference with results obtained from the random-effects model.

**UFH VS CONTROL**

Pooled results demonstrated reductions in the risk of DVT (RR, 0.33; 95% CI, 0.26-0.42) and PE (RR, 0.64; 95% CI, 0.50-0.82) among those receiving UFH. No mortality difference was seen between the UFH and control groups (RR, 0.95; 95% CI, 0.88-1.02). Therapy was associated with an increased risk of total bleeding (RR, 3.11; 95% CI, 2.44-3.96).

A UFH dosage of 5000 U 3 times daily was associated with a greater reduction in the risk of DVT than a UFH dosage of 5000 U twice daily (RR, 0.27; 95% CI, 0.20-0.36; and RR, 0.52; 95% CI, 0.28-0.96, respectively). When the random-effects model was used, the decreased risk of DVT associated with a UFH dosage of 5000 U twice daily became statistically nonsignificant (RR, 0.41; 95% CI, 0.10-1.73).

**LMWH VS CONTROL**

Compared with the control, LMWH was associated with a reduced risk of DVT (RR, 0.56; 95% CI, 0.45-0.70) and PE (RR, 0.37; 95% CI, 0.21-0.64). An increased risk of total bleeding (RR, 1.51; 95% CI, 1.31-1.74), major imaging, and chest radiography. In some studies, PE was diagnosed clinically or at autopsy. The method used was not specified in some studies, whereas in others described the number of events or episodes observed. When possible, we used data for the number of patients who experienced the relevant outcomes. Furthermore, in their results sections, some authors did not provide data for the total number of patients who experienced bleeding yet reported subcategories of this outcome separately. When this occurred, we added the patients or episodes into the different subcategories to obtain a combined figure for the purposes of our analysis of total bleeding. Major and minor bleeding episodes were also occasionally reported in terms of subcategories.

### Figure 1. Quality of reporting of meta-analyses flow diagram of studies evaluated for inclusion in the meta-analysis. LMWH indicates low-molecular-weight heparin or heparinoid; UFH, unfractionated heparin.

with UFH and 1 compared fondaparinux sodium with placebo (Table 2).

Several different modes of investigation were used to diagnose DVT among the trials. Venography, iodine 125 fibrinogen scanning, impedance plethysmography, and ultrasonography were all used. Alternatively, in some cases DVT was diagnosed either clinically or at autopsy. In one study, the method used to diagnose reported DVT was not specified.

Methods used to diagnose PE were ventilation and perfusion lung scanning, pulmonary angiography, spiral computed tomography, and magnetic resonance imaging.

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References 9, 37, 40-42, 47-49, 66, 67, 69, 70, 72.

References 9, 37, 40, 47, 49, 57, 58, 68-72.

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<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>No. of Participants</th>
<th>Population, Age, y</th>
<th>Drug</th>
<th>Dosage and Route of Administration</th>
<th>Comparator Drug</th>
<th>Dosage and Route of Administration</th>
<th>Length of Treatment, d</th>
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<tr>
<td>Handley et al.50, 1972</td>
<td>R, C</td>
<td>60</td>
<td>Myocardial infarction, &lt;70</td>
<td>Heparin</td>
<td>5000 U IV (loading dose) followed by 20 000 U IV twice daily</td>
<td>No heparin</td>
<td>NA</td>
<td>14</td>
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<td>Handley,51 1972</td>
<td>R, C</td>
<td>70</td>
<td>Myocardial infarction, 58.3 (mean, heparin), 59.6 (mean, control)</td>
<td>Heparin</td>
<td>5000 U IV and 7500 U SC as soon as possible, then 7500 U SC twice daily</td>
<td>No heparin</td>
<td>NA</td>
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<td>Gallus et al.52, 1973</td>
<td>R, C</td>
<td>350 (78 relevant)</td>
<td>Medical patients with suspected myocardial infarction, &gt;40</td>
<td>Heparin</td>
<td>5000 U SC 3 times daily</td>
<td>No heparin</td>
<td>NA</td>
<td>Until mobile</td>
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<td>Warlow et al.53, 1973</td>
<td>R, DB, PC</td>
<td>146</td>
<td>Myocardial infarction, 40-75</td>
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<td>5000 U SC twice daily</td>
<td>Placebo</td>
<td>NA</td>
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<td>Emerson and Marks.54, 1977</td>
<td>R, C</td>
<td>78</td>
<td>Medical patients with suspected myocardial infarction, &gt;40</td>
<td>Heparin</td>
<td>Low dose SC</td>
<td>No heparin</td>
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<td>McCarthy et al.55, 1977</td>
<td>R, C</td>
<td>32</td>
<td>Acute stroke, elderly</td>
<td>Heparin calcium</td>
<td>5000 U SC 3 times daily</td>
<td>No heparin</td>
<td>NA</td>
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<tr>
<td>Pitt et al.56, 1980</td>
<td>R, PC</td>
<td>108 (73 relevant)</td>
<td>Stroke, 7.2 (mean)</td>
<td>Heparin calcium</td>
<td>5000 U IV twice daily</td>
<td>Placebo</td>
<td>NA</td>
<td>2 (heparin), 2-3 (placebo)</td>
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<td>Gelmers.57 1980</td>
<td>R, C</td>
<td>104</td>
<td>Stroke, 7.2 (mean)</td>
<td>Heparin sodium</td>
<td>SC 3 times daily; started with 5000 U; dosage increased or decreased in increments of 500 U to maintain daily aPTT levels between 30.0 and 39.9 s</td>
<td>No heparin</td>
<td>NA</td>
<td>28 or until discharge</td>
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<tr>
<td>Belch et al.58, 1981</td>
<td>R, C</td>
<td>100</td>
<td>Heart failure and/or chest infection, 40-80</td>
<td>Heparin</td>
<td>5000 U SC 3 times daily</td>
<td>No prophylaxis</td>
<td>NA</td>
<td>Until fully mobile</td>
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<td>McCarthy and Turner.59, 1986</td>
<td>R, C</td>
<td>305</td>
<td>Heart failure and/or chest infection, 40-80</td>
<td>Heparin</td>
<td>5000 U SC 3 times daily</td>
<td>No heparin</td>
<td>NA</td>
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<td>Zawilska et al.60, 1989</td>
<td>R, C</td>
<td>103</td>
<td>Acute myocardial infarction, 58 (mean, heparin), 59 (mean, control)</td>
<td>Heparin sodium</td>
<td>5000 U SC twice daily</td>
<td>No heparin</td>
<td>NA</td>
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<td>Pambianco et al.61, 1995</td>
<td>R, C</td>
<td>360 (235 relevant)</td>
<td>Stroke, 7.2 (mean)</td>
<td>Heparin sodium</td>
<td>SC 3 times daily; started with 5000 U; dosage increased or decreased in increments of 500 U to maintain daily aPTT levels between 30.0 and 39.9 s</td>
<td>No heparin</td>
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<td>Gardlund et al.62, 1996</td>
<td>R, C, MC</td>
<td>11 693</td>
<td>Infectious diseases, ≥55</td>
<td>Heparin sodium</td>
<td>5000 U SC twice daily</td>
<td>No prophylaxis</td>
<td>NA</td>
<td>Stopped at discharge, after maximum of 21 d or if a predefined contraindication occurred</td>
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<td>International Stroke Trial.63, 1997</td>
<td>R, C, MC</td>
<td>19 435</td>
<td>Acute ischemic stroke, 61% &lt;70</td>
<td>Heparin calcium or heparin sodium</td>
<td>5000 or 12 500 IU SC twice daily</td>
<td>No heparin</td>
<td>NA</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>No. of Participants</th>
<th>Population, Age, y</th>
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<th>Comparator Drug</th>
<th>Dosage and Route of Administration</th>
<th>Length of Treatment, d</th>
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<tr>
<td>Dahan et al.64, 1986</td>
<td>R, DB, PC</td>
<td>270</td>
<td>Hospitalized medical, &gt;65</td>
<td>Enoxaparin</td>
<td>60 mg SC once daily</td>
<td>Placebo</td>
<td>NA</td>
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<td>Turpie et al.65, 1987</td>
<td>R, DB, PC, MC</td>
<td>75</td>
<td>Acute thrombotic stroke, 69.6 (mean, danaparoid sodium), 68.3 (mean, placebo)</td>
<td>Danaparoid sodium</td>
<td>Loading dose of 1000 U anti-Xa IV followed by a fixed dose of 750 anti-Xa U SC twice daily</td>
<td>Placebo</td>
<td>NA</td>
<td>14 or until discharge if earlier</td>
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<td>Prins et al.66, 1989</td>
<td>R, DB, PC</td>
<td>60</td>
<td>Acute ischemic stroke, 71-80 (median)</td>
<td>Dalteparin</td>
<td>2500 U anti-Xa SC twice daily</td>
<td>Placebo</td>
<td>NA</td>
<td>14</td>
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<td>Sandset et al.67, 1990</td>
<td>R, DB, PC</td>
<td>103</td>
<td>Acute ischemic stroke</td>
<td>Dalteparin</td>
<td>0.30-0.55 mL SC once daily (based on body weight)</td>
<td>Placebo</td>
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<td>14 or until discharge if earlier</td>
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<td>Key et al.68, 1995</td>
<td>R, DB, PC, MC</td>
<td>312</td>
<td>Acute ischemic stroke, ≥80</td>
<td>Nadroparin</td>
<td>4100 U anti-Xa SC twice daily or 4100 U anti-Xa SC once daily</td>
<td>Placebo</td>
<td>NA</td>
<td>10</td>
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<tr>
<td>Bergmann and Caulin.69, 1996</td>
<td>R, DB, PC, MC</td>
<td>2472</td>
<td>Hospitalized medical, 76 (mean)</td>
<td>Nadroparin</td>
<td>7500 U anti-Xa once daily</td>
<td>Placebo</td>
<td>NA</td>
<td>Up to 21</td>
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(continued)
bleeding (RR, 1.92; 95% CI, 1.32-2.78), minor bleeding (RR, 1.40; 95% CI, 1.17-1.67), and injection site hema-
toma (RR, 2.04; 95% CI, 1.06-3.93) was observed with therapy. (Figure 3). When the random-effects model was used, the increased risk of major bleeding and injection site hematoma became statistically nonsignificant. No difference in mortality (RR, 1.02; 95% CI, 0.88-1.19) or thrombocytopenia (RR, 1.10; 95% CI, 0.69-1.77) was found between the 2 groups.

LMWH VS UFH

Compared with UFH, LMWH was associated with a reduced risk of DVT (RR, 0.68; 95% CI, 0.52-0.88) and injection site hematoma (RR, 0.47; 95% CI, 0.36-0.62). No statistically significant differences were observed between the 2 agents with respect to PE (RR, 0.57; 95% CI, 0.25-1.34), mortality (RR, 1.16; 95% CI, 0.85-1.59), total bleeding (RR, 0.83; 95% CI, 0.60-1.14), major bleeding

<table>
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<th>Source</th>
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<th>No. of Participants</th>
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<th>Drug</th>
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<th>Comparator Drug</th>
<th>Dosage and Route of Administration</th>
<th>Length of Treatment, d</th>
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<tr>
<td>Hommel et al, 1998</td>
<td>R, DB, PC, MC</td>
<td>767</td>
<td>Ischemic stroke</td>
<td>Nadroparin</td>
<td>86 IU/kg once daily or 86 IU/kg twice daily IV bolus dose followed by continuous infusion; rates of the infusion were adjusted after 24 h to maintain the anti-Xa activity at 0.6 to 0.8 U/mL anti-Xa</td>
<td>Placebo</td>
<td>NA</td>
<td>10</td>
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<tr>
<td>TOAST, 1998</td>
<td>R, DB, PC, MC</td>
<td>1281</td>
<td>Acute ischemic stroke, 18-85</td>
<td>Danaparoid sodium</td>
<td>120 IU/kg anti-Xa SC twice daily</td>
<td>Placebo</td>
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<td>Samama et al, 1999</td>
<td>R, DB, PC</td>
<td>1102</td>
<td>Hospitalized medical, &gt;40</td>
<td>Enoxaparin</td>
<td>40 mg SC once daily or 20 mg SC once daily</td>
<td>Placebo</td>
<td>NA</td>
<td>6-14</td>
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<td>Leizorovicz et al, 2004</td>
<td>R, DB, PC, MC</td>
<td>3706</td>
<td>Hospitalized medical, &gt;40</td>
<td>Dalteparin</td>
<td>5000 IU SC once daily</td>
<td>Placebo</td>
<td>NA</td>
<td>14</td>
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</table>

**LMWH vs UFH**

- **Harenberg et al, 1990**
  - R, DB, C: Medical, 40-80
  - LMWH: 1.500 U aPTT SC once daily
  - Comparator: Heparin sodium
  - Length of Treatment: 7-12 (mean)

- **Scala et al, 1990**
  - R, C: Acute myocardial infarction, 69 (mean)
  - Dalteparin: 750 U anti-Xa SC twice daily
  - Comparator: Standard heparin
  - Length of Treatment: 7

- **Turpie et al, 1992**
  - R, DB, C, MC: Acute ischemic stroke, 72.3 (mean, danaparoid sodium), 72.5 (mean, UFH)
  - Danaparoid sodium: 750 U anti-Xa SC twice daily
  - Comparator: Heparin sodium
  - Length of Treatment: 14 or until discharge if earlier

- **Dumas et al, 1994**
  - R, DB, C, MC: Acute ischemic stroke, 72.6 ± 12.1 (range, danaparoid sodium), 72.9 ± 13.1 (range, UFH)
  - Danaparoid sodium: 1250 U anti-Xa SC once daily
  - Comparator: Heparin sodium USP
  - Length of Treatment: 9-13

- **Bergmann and Neubauer et al, 1996**
  - R, DB, C, MC: Medical, ≥65
  - Enoxaparin: 20 mg SC once daily
  - Comparator: Heparin calcium
  - Length of Treatment: 10

- **Harenberg et al, 1996**
  - R, DB, C, MC: Medical, 50-80
  - Nadroparin: 36 mg SC once daily
  - Comparator: Heparin calcium
  - Length of Treatment: 8-11

- **Lechner et al, 1996**
  - R, DB, C, MC: Medical, ≥18
  - Danaparoid sodium: 40 mg SC once daily
  - Comparator: Heparin calcium
  - Length of Treatment: 7

- **Hillborn et al, 2002**
  - R, DB, C, MC: Acute ischemic stroke, 18-90
  - Enoxaparin: 40 mg SC once daily
  - Comparator: Heparin calcium
  - Length of Treatment: 10 ± 2 or until discharge if earlier

- **Kleber et al, 2003**
  - R, C, MC: Severe respiratory disease or heart failure, ≥18
  - Enoxaparin: 40 mg SC once daily
  - Comparator: Heparin calcium
  - Length of Treatment: 10 ± 2

- **Diener et al, 2006**
  - R, DB, C, MC: Acute ischemic stroke, 18-85
  - Certoparin: 3000 U anti-Xa SC once daily
  - Comparator: Heparin sodium
  - Length of Treatment: 12-16

**Cohen et al, 2006**
- R, DB, PC: Medical, ≥60
- Fondaparinux: 2.5 mg SC once daily
- Comparator: Placebo
- Length of Treatment: 6-14

### Abbreviations
- anti-Xa: selective factor Xa inhibitor
- aPTT: activated partial thromboplastin time
- C: controlled
- COPD: chronic obstructive pulmonary disease
- DB: double-blind
- IV: intravenous
- LMWH: low-molecular-weight heparin or heparinoid
- MC: multicenter
- NA: details not available
- PC: placebo-controlled
- R: randomized
- SC: subcutaneous
- TOAST: Trial of ORG 10172 in Acute Stroke Treatment
- UFH: unfractionated heparin


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bdominal bleeding (RR, 0.61; 95% CI, 0.34-1.10), or thrombocytopenia (RR, 0.25; 95% CI, 0.05-1.16) (Figure 4).

PROPHYLAXIS VS NO PROPHYLAXIS

Prophylaxis with UFH, LMWH, or fondaparinux was associated with a reduced risk of DVT (RR, 0.45; 95% CI, 0.39-0.53) and PE (RR, 0.57; 95% CI, 0.45-0.72) and an increased risk of total bleeding (RR, 1.90; 95% CI, 1.69-2.14). Prophylaxis did not have an effect on mortality (RR, 0.95; 95% CI, 0.89-1.02).

SENSITIVITY ANALYSES

When 2 trials were singly removed in turn from the analysis of UFH vs the control for the outcome of PE using the random-effects method, the reduction in risk observed with UFH became statistically nonsignificant.

Analysis of the UFH dosage of 5000 U twice daily vs the control for DVT was also influenced by the removal of 2 trials when singly removed, with the association no longer significant in either the fixed-effects or random-effects method. Furthermore, for LMWH vs the control, removal of a different study made the outcome for minor bleeding no longer significant when the random-effects method was applied.

PUBLICATION BIAS

Funnel plots showed some asymmetry, indicating the potential for publication bias (Figure 5).

SELECTIVE FACTOR Xa INHIBITORS

The trial that met the eligibility criteria for inclusion in this meta-analysis found that fondaparinux was effec-
Fig. 2. Meta-analysis of deep venous thrombosis (DVT), pulmonary embolism (PE), and mortality when comparing unfractionated heparin (UFH) with the control. Results were obtained using the fixed-effects method. Sizes of data markers relate to the weights assigned to each trial. Test for heterogeneity: DVT, P = .02; DVT (UFH, 5000 U twice daily, vs control), P = .02; DVT (UFH, 5000 U 3 times daily, vs control), P = .50; PE, P = .06; and mortality, P = .65. CI indicates confidence interval; IST, International Stroke Trial. * DVT found at autopsy that caused or contributed to death. † Fatal PE.

This meta-analysis has shown that UFH and LMWH are both associated with a reduced risk of VTE in
medical patients, with LMWH being more effective in preventing DVT than UFH when considering trials that directly compared the 2 agents. The UFH dosage of 5000 U 3 times daily was more effective than the

UFH dosage of 5000 U twice daily in reducing the risk of DVT.

Despite the observed reduction in VTE events, thromboprophylaxis did not affect mortality. This result may be accounted for by several factors. The patients who participated in the trials were generally un-
well, with multiple comorbidities and a high in-hospital mortality rate (up to 8.19% in our analysis). It is therefore likely that a large proportion of patient deaths were attributable to causes other than VTE events. Furthermore, it is likely that many of the DVTs detected by the investigators either did not embolize at all or did not do so during the study period. It is also possible that a considerable proportion of the reported PEs were not fatal events. Although UFH and LMWH were associated with an increased risk of bleeding, it is unlikely that these episodes, many of which were minor, led to an increase in fatalities that would offset the reduction in mortality due to VTE. This theory is substantiated by the minimal reporting of fatal hemorrhagic episodes in the individual trials.

In contrast to our study, a retrospective database analysis found that thromboprophylaxis reduces mortality. Several possible explanations exist for this discrepancy between results. Notably, randomization was not undertaken in the database analysis, and although results were adjusted for age, sex, and severity of illness, many other factors that contribute to VTE risk were not taken into account. Furthermore, as acknowledged by the investigators of the database analysis, the results may have been affected by treatment bias. For example, as the authors explained, some patients may not have received prophylaxis because their prognosis was poor and physicians believed it would not provide any benefit. Additionally, unlike in the retrospective study, in many of the trials included in our meta-analysis, patients were routinely screened at an early stage of DVT. Treatment of detected DVTs, when undertaken, would likely have reduced the number of PEs and deaths that occurred, potentially minimizing a difference in mortality between the prophylaxis and control groups.

A limitation of our analysis is that the patient population is not homogeneous. Participants in the trials had a diverse range of medical conditions and risk factors for VTE. Although UFH and LMWH were associated with an increased risk of bleeding, it is unlikely that these episodes, many of which were minor, led to an increase in fatalities that would offset the reduction in mortality due to VTE. This theory is substantiated by the minimal reporting of fatal hemorrhagic episodes in the individual trials.

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A limitation of our analysis is that the patient population is not homogeneous. Participants in the trials had a diverse range of medical conditions and risk factors for VTE. However, although not ideal, we believe it acceptable to pool results from the various trials given the natural diversity of patients in a general medical ward. One must nevertheless be wary of the heterogeneity of the patient group analyzed when applying the results of this analysis to particular patient groups in the clinical setting. A further limitation of this study is that the type of LMWH used was not consistent among the trials. Any potential differences in efficacy or safety among these agents would not be reflected in the pooled analyses.

A meta-analysis published in 2000 investigated the efficacy and safety of pharmacological agents used for VTE prophylaxis in medical patients. The authors of that meta-analysis stated that their study lacked sufficient power to detect a difference in efficacy between LMWH and UFH. In contrast to our meta-analysis, the 2000 study found that LMWH reduced the risk of major bleeding compared with UFH. The inconsistency of definitions of major bleeding in the individual trials analyzed in both meta-analyses could potentially contribute to the contrasting results observed between the 2 analyses. Furthermore, our study differs from the previous meta-analysis because it considers patients with acute myocardial infarction and ischemic stroke, who represent an important co-
hort of medical patients, and includes several large trials that have been completed since the 2000 publication.

Our meta-analysis shows that UFH and LMWH reduce the risk of VTE, with LMWH being more effective in preventing DVT when the 2 agents are directly compared. Our results indicate that if UFH is to be used, a dose of 5000 U 3 times daily is preferable to 5000 U twice daily. We believe that routine prophylactic anticoagulation has an important place in the medical setting. Although such therapy may not necessarily decrease mortality among hospitalized medical patients, it will reduce the occurrence of DVT and PE and therefore the burden of illness currently caused by these events.

Accepted for Publication: February 2, 2007.
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Financial Disclosure: None reported.

Funding/Support: This study was supported by a Centre of Clinical Research Excellence grant from the National Health and Medical Research Council of Australia.

REFERENCES


