Dosing Frequency of Unfractionated Heparin Thromboprophylaxis: A Meta-analysis

Olivia J. Phung, Susan R. Kahn, Deborah J. Cook and Mohammad Hassan Murad

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Dosing Frequency of Unfractionated Heparin Thromboprophylaxis

A Meta-analysis

Olivia J. Phung, PharmD; Susan R. Kahn, MD; Deborah J. Cook, MD, MSc(Epi); and Mohammad Hassan Murad, MD, MPH

Background: In medical patients, it is unclear whether thromboprophylaxis with low-dose unfractionated heparin (UFH) should be administered bid or tid.

Methods: This study was a mixed-treatment comparison meta-analysis of randomized control trials that enrolled hospitalized nonsurgical patients at risk for VTE and compared UFH bid, UFH tid, or low-molecular-weight heparin (LMWH) to one another or to an inactive control subject. DVT, pulmonary embolism (PE), major bleeding, and death were measured. A Bayesian framework using a random-effects model was applied.

Results: Sixteen trials with moderate methodologic quality enrolling 27,667 patients contributed to this analysis. The relative risk and 95% credible intervals comparing UFH tid to UFH bid for DVT, PE, death, and major bleeding were 1.56 (0.64-4.33), 1.67 (0.49-208.09), 1.17 (0.72-1.95), and 0.89 (0.08-7.05), respectively. When compared with either dose of UFH, the use of LMWH has an effect similar to UFH on all four outcomes.

Conclusions: Moderate-quality evidence suggests that subcutaneous UFH bid and UFH tid do not differ in effect on DVT, PE, major bleeding, and mortality. Either of the two dosing regimens of UFH or LMWH appears to be a reasonable strategy for thromboprophylaxis in medical patients. A future randomized trial comparing the two doses of UFH is very unlikely, considering the very large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small.

Abbreviations: LMWH = low-molecular-weight heparin; MTC = mixed-treatment comparison; PE = pulmonary embolism; RCT = randomized controlled trial; UFH = unfractionated heparin

Hospitalized medical patients have unique risks for VTE, and treatment recommendations for this population differ from surgical patients. Low-dose unfractionated heparin (UFH) treatment is among the pharmacologic thromboprophylaxis strategies recommended for medical patients. However, it is unclear whether UFH dosing should be given bid or tid because no head-to-head trials of bid vs tid have been conducted. Using a test of interaction, a previous meta-analysis evaluated the effect of UFH bid vs tid dosing on VTE events per 1,000 patients, analyzing trials that compared UFH to either placebo or low-molecular-weight heparin (LMWH) (pooling the placebo and LMWH arms together as their comparator to UFH). This indirect analysis showed no significant difference between bid vs tid dosing on efficacy but...
a significantly increased risk of major bleeding with tid dosing.

We extended this work by analyzing more recently published randomized controlled trials (RCTs). We also used a mixed-treatment comparison (MTC) meta-analysis, which analyzes all arms independently in a single statistical model, allowing the pooling of similar treatment arms, regardless of comparator, while preserving the randomization of the original trials. This method can be used to determine the comparative effectiveness and harms between bid and tid dosing of UFH.

MATERIALS AND METHODS

Eligibility Criteria and Data Sources

We considered studies eligible for this analysis if they were RCTs that (1) enrolled hospitalized medical patients (nonsurgical patients) at risk for VTE, (2) compared at least one of the interventions of interest to another or to an inactive control subject (UFH bid, UFH tid, LMWH), and (3) measured the outcomes of interest (DVT, pulmonary embolism [PE], major bleeding, and death). Major bleeding was defined by the individual trial investigators.

Relevant RCTs were identified by the American College of Chest Physicians guideline expert panel charged with developing clinical practice guidelines for the prevention of VTE in nonsurgical patients. The panel obtained RCTs from two well-conducted systematic reviews that focused on medical patients. The first is a Cochrane database review by Alkilani et al with a database search date to April 2009 that excluded patients with stroke and myocardial infarction. The second is by Dentali et al with a database search date to September 2006 that only excluded patients with stroke. Both reviews considered patients with stroke to be a particularly high-risk subgroup to the extent that generalization of efficacy and harm data to other medical patients would be inappropriate. The expert panel updated the literature searches through March 2010, which resulted in retrieving one additional trial that compared certoparin to UFH. Study characteristics, trial quality indicators, and event rates. In all cases, a random-effects model was fitted. Residual deviance similar to the number of unconstrained data points (25 and 26, respectively).

Statistical Analysis

We conducted an MTC meta-analysis to compare the different thromboprophylaxis strategies. In addition to analyzing the direct within-trial comparisons between the two randomization arms, the MTC framework incorporates indirect comparisons constructed from two RCTs that have one randomization arm in common. This type of analysis safeguards each within-trial randomized comparison while analyzing all available comparisons.

We conducted MTC analyses using a Bayesian Markov Chain Monte Carlo method and fitted in the freely available Bayesian software WinBUGS (www.mrc-bsu.cam.ac.uk/bugs). MTC methods were used to calculate the relative risks for DVT, PE, death, and major bleeding for all treatments relative to every other arm within the model, with accompanying 95% credible interval. In all cases, a random-effects model was fitted. Residual deviance was calculated for each outcome. Within a Bayesian framework, a residual deviance that approximates the number of unconstrained data points within the model suggests a good fit.

RESULTS

Trial Characteristics

We included a total of 16 trials (27,667 patients) in the meta-analysis. Thirteen trials reported results for the outcome of DVT, 16 reported PE, 14 reported major bleeding, and 12 reported death. In Figure 1, we present the overall network of direct comparisons. The duration of treatment and follow-up of outcomes after initiation of prophylaxis ranged from 6 to 90 days (median, 20 days). Tables 1 and 2 summarize the trial characteristics, quality indicators, and event rates. Patients enrolled in the trials were eligible for prophylaxis because of acute medical illnesses resulting in bed confinement due to various causes, including heart failure, respiratory disease, or infection. Study quality was moderate in most trials, with some high-quality trials.

Quantitative Synthesis

DVT: In the MTC meta-analysis, each prophylactic strategy significantly reduced the risk of DVT compared with inactive control subjects. The risk reductions ranged from 58% to 72% (Figs 2, 3; Table 3). There were no statistically significant differences among any of the active prophylactic strategies. Good model fit for the DVT outcome was suggested by a calculated residual deviance similar to the number of unconstrained data points.

Pulmonary Embolism: None of the prophylactic strategies significantly reduced the risk of PE compared with inactive control subjects; however, each showed a favorable trend as reflected in risk reductions ranging from 46% to 67% (Figs 2, 4; Table 3). No differences were seen among the active prophylactic strategies. The outcome of PE also exhibited good model fit, with calculated residual deviance similar to the number of unconstrained data points.
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>No.</th>
<th>Indication for Prophylaxis</th>
<th>Treatments</th>
<th>Duration of Follow-up, d</th>
<th>Allocation Concealment</th>
<th>Double Blind</th>
<th>Description of Withdrawals</th>
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<tbody>
<tr>
<td>Gallus et al 1973</td>
<td>26</td>
<td>Heart failure</td>
<td>UFH 5,000 units tid Control subjects (no placebo)</td>
<td>&lt;28</td>
<td>Yes</td>
<td>Unclear</td>
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<td>Belch et al 1981</td>
<td>100</td>
<td>Heart failure, chest infection</td>
<td>UFH 5,000 units tid Control subjects (no placebo)</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dahan et al 1986</td>
<td>270</td>
<td>Congestive heart failure (NYHA class III-IV), acute or respiratory infections disease</td>
<td>Enoxaparin 60 mg daily Placebo</td>
<td>10</td>
<td>Not defined</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ibarra-Pérez et al 1988</td>
<td>85</td>
<td>Pulmonary disease and immobilized for &gt;3 d</td>
<td>UFH 5,000 units bid Control subjects (no placebo)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Forette and Wolmark 1995</td>
<td>295</td>
<td>Acute medical illness for an estimated minimum duration of 4 wk, recent transient reduced mobility</td>
<td>Nadroparin 3,075 units daily UFH 5,000 tid</td>
<td>28</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bergmann and Caulin 1996</td>
<td>2,474</td>
<td>Acute medical illness and confined to bed</td>
<td>Nadroparin 7,500 units daily Placebo</td>
<td>21</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
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<tr>
<td>Bergmann and Neuhart 1996</td>
<td>442</td>
<td>Acute medical illness leading to reduced mobility</td>
<td>Enoxaparin 20 mg daily UFH 5,000 units bid</td>
<td>&lt;11</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Gärdhms 1996</td>
<td>11,693</td>
<td>Infectious disease</td>
<td>UFH 5,000 units tid Control subjects (no placebo)</td>
<td>60</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Lechner et al 1996</td>
<td>939</td>
<td>Acute medical illness and at least one additional risk factor, expected immobilization for more than one-half of the daytime for the study period (7 d)</td>
<td>Enoxaparin 40 mg daily UFH 5,000 units tid</td>
<td>7</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Samama et al 1999</td>
<td>738</td>
<td>Acute medical illness, not immobilized for &gt;3 d</td>
<td>Enoxaparin 40 mg daily Placebo</td>
<td>6-14</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fraisse et al 2000</td>
<td>223</td>
<td>Acute decompensated COPD with mechanical ventilation</td>
<td>Nadroparin 3,800-5,700 units daily Placebo</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Kleber et al 2003</td>
<td>665</td>
<td>Severe respiratory disease or heart failure and confined to bed for more than two-thirds of each day</td>
<td>Enoxaparin 40 mg daily UFH 5,000 units tid</td>
<td>8-12</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Leizorovicz et al 2004</td>
<td>3,706</td>
<td>Acute medical illness requiring projected hospitalization ≥4 d and had ≤3 d of prior immobilization</td>
<td>Dalteparin 5,000 units daily Placebo</td>
<td>14</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mahé et al 2005</td>
<td>2,472</td>
<td>Congestive heart failure (NYHA class III-IV), acute or respiratory disease, nonpulmonary sepsis, cancer</td>
<td>Nadroparin 7,500 units daily Control subjects (not specified)</td>
<td>21</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Lederle et al 2006</td>
<td>280</td>
<td>Hospitalization in general medical unit</td>
<td>Enoxaparin 40 mg daily Control subjects (not specified)</td>
<td>90</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Riess et al 2010</td>
<td>3,239</td>
<td>Acute medical illness with a significant decrease in mobility (bedridden or only able to walk short distances)</td>
<td>Certoparin 3,000 units daily UFH 5,000 units tid</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

LMWH = low-molecular-weight heparin; NYHA = New York Heart Association; UFH = unfractionated heparin.
Table 3. Good model fit was suggested by a calculated residual deviance similar to the number of unconstrained data points (27 and 28, respectively).

**Discussion**

We conducted a Bayesian MTC of UFH bid vs tid using evidence obtained indirectly from comparisons of UFH bid or tid against inactive control subjects and LMWH. Our results suggest that both treatments
use of LMWH has a similar effect as UFH on all four outcomes. Strengths of this analysis are the comprehensive literature search, explicit trial selection criteria, and assessment of trial methodologic quality. We statistically pooled results for four major outcomes of relevance to clinicians focusing on VTE prevention. We transparently reported both direct and indirect comparisons of thromboprophylactic strategies. As for the latter, the MTC meta-analysis allowed for an indirect comparison of UFH tid vs UFH bid. A direct comparison is not possible because head-to-head comparative dosing trials of UFH do not exist. The MTC meta-analysis also provided an integration of direct and indirect comparisons of LMWH to either dose of UFH, strengthening the preexisting head-to-head trial data of LMWH and UFH. The evidence the present study generated can inform decisions about various thromboprophylaxis strategies, taking into account other issues such as patient preference and administrative costs.

Limited inferences provided by this meta-analysis stem from imprecision in the estimates (due to a relatively small number of events), which yields fairly wide confidence limits. In addition, there is no current (bid and tid) are more effective than the inactive control conditions but are similar to each other in terms of the relative risk of DVT, PE, major bleeding, and mortality. Compared with either dose of UFH, the

![Image of forest plot diagrams](image-url)

**Figure 2.** Forest plot diagram of results of mixed-treatment comparison meta-analysis of trials evaluating LMWH, UFH, or control subjects in a nonsurgical hospitalized population. The squares represent the pooled relative risk for each type of intervention compared with control subjects. Error bars represent 95% credible intervals. PE = pulmonary embolism. See Figure 1 legend for expansion of abbreviations.

![Image of network diagram](image-url)

**Figure 3.** Network diagram of results of mixed-treatment comparison meta-analysis on DVT of trials evaluating LMWH, UFH, or control subjects in a nonsurgical hospitalized population. Solid lines represent the presence of direct evidence along with indirect evidence. Results are reported as relative risks and 95% credible intervals. Arrows represent the favored drug in the mixed-treatment comparison meta-analysis (decreased risk of DVT), and results reported are referent to the arrow origin. Thus, results may not correspond to numerical results reported elsewhere. Results referent to the second agent in a comparison equal 1/relative risk. See Figure 1 legend for expansion of abbreviations.

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We believe that a future peer-reviewed, funded RCT comparing UFH bid vs tid is very unlikely to be conducted, considering the very large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small. Furthermore, industry funding for trials of generic inexpensive pharmacological agents will be of low priority, particularly when corporate directives favor testing newer drugs such as LMWH and oral thromboprophylactic agents.

The prior meta-analysis by King et al. showed trends toward increased efficacy with tid dosing on PE and significant increases in major bleeding with tid vs bid dosing. The duration of action for UFH ranges from 4.5 to 7.5 h based on a 1.5-h elimination half-life, suggesting favor for tid dosing. However, the present study results from an MTC meta-analysis did not support previous conclusions, instead showing no significant differences between the dosing frequencies and outcomes. Our results may have differed because of differences in statistical technique and inclusion of consensus on how to rate the quality of evidence arising from indirect comparisons. Such comparisons are unlikely to represent high-quality evidence because of the indirectness of the comparisons. However, when no head-to-head comparative trials exist, we believe that indirect comparisons are better than no comparative analyses at all. Furthermore, the results generated by an MTC meta-analysis may be considered of moderate quality, particularly when either large treatment effects or a dose-response relationship is observed, which typically strengthen inferences. Most patients enrolled in the included studies were at low risk of bleeding and had limited comorbidities, which likely influenced the overall low rates of major bleeding reported in the trials. Other hospitalized patients, such as those in the medical ICU, may be more susceptible to the bleeding risk of thromboprophylaxis. Even though our results did not show statistically significant differences in bleeding comparing the two UFH dosing regimens, major bleeding is still a concern in all patients, and careful monitoring is required.

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newer trials. Some of the differences could be attributed to the pooling of dissimilar control arms in the meta-analysis by King et al., where the LMWH, placebo, and control conditions were pooled together as the comparator to UFH. The present study MTC meta-analysis minimizes this effect by treating LMWH and placebo or control as two separate comparators and provides a more accurate estimation of the comparative efficacy of the two dosing frequencies.

In summary, moderate-quality evidence suggests that subcutaneous UFH bid and UFH tid have similar effects on DVT, PE, major bleeding, and mortality. Therefore, convenience and cost may influence decisions about UFH dosing. All heparin thromboprophylaxis strategies studied in these RCTs significantly decrease risk of DVT and suggest a trend toward lowering risk of PE without significantly affecting risk of bleeding or death.

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Author contributions: Dr Phung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Phung contributed to the development of the protocol, data collection, statistical analysis, and writing and approval of the final manuscript. Dr Kahn contributed to the development of the research idea, literature search, and writing and approval of the final manuscript. Dr Cook contributed to the development of the research idea, literature search, and writing and approval of the final manuscript. Dr Murad contributed to the development of the research idea and protocol, literature search, data collection, statistical analysis, and writing and approval of the final manuscript.

Financial/conflicts of interest disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Kahn is the deputy editor of the upcoming ninth edition of the American College of Chest Physicians (ACCP) consensus guidelines on antithrombotic therapy for the chapter titled “Prevention of VTE in Nonsurgical Patients” and is a recipient of a National Research Scientist Award from the Fonds de la Recherche en Santé du Québec. Dr Cook recently completed a peer-reviewed, funded randomized control trial comparing unfractionated heparin to low-molecular-weight heparin in an ICU, with study drugs provided by Pfizer Inc and Eisai Inc and is a Canada Research Chair of the Canadian Institutes of Health Research. Drs Kahn, Cook, and Murad are panelists for the ACCP Antithrombotic and Thrombolytic Guidelines. Dr Phung has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES


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