Annals of Internal Medicine | Review

Meta-analysis: Anticoagulant Prophylaxis to Prevent Symptomatic Venous Thromboembolism in Hospitalized Medical Patients

Francesco Dentali, MD; James D. Douketis, MD; Monica Gianni, MD; Wendy Lim, MD; and Mark A. Crowther, MD, MSc

Background: Underutilization of anticoagulant prophylaxis may be due to lack of evidence that prophylaxis prevents clinically important outcomes in hospitalized medical patients at risk for venous thromboembolism.

Purpose: To assess the effects of anticoagulant prophylaxis in reducing clinically important outcomes in hospitalized medical patients.

Data Sources: MEDLINE, EMBASE, and Cochrane databases were searched to September 2006 without language restrictions.

Study selection: Randomized trials comparing anticoagulant prophylaxis with no treatment in hospitalized medical patients.

Data Extraction: Any symptomatic pulmonary embolism (PE), fatal PE, symptomatic deep venous thrombosis, all-cause mortality, and major bleeding. Pooled relative risks and associated 95% CIs were calculated. For treatment effects that were statistically significant, the authors determined the absolute risk reduction and the number needed to treat for benefit (NNT_B) to prevent an outcome.

Data Synthesis: 9 studies ($n = 19\,958$) were included. During anticoagulant prophylaxis, patients had significant reductions in any PE (relative risk, 0.43 [CI, 0.26 to 0.71]; absolute risk reduction, 0.29%; NNT_B, 345) and fatal PE (relative risk, 0.38 [CI, 0.21 to 0.69]; absolute risk reduction, 0.25%; NNT_B, 400), a nonsignificant reduction in symptomatic deep venous thrombosis (relative risk, 0.47 [CI, 0.22 to 1.00]), and a nonsignificant increase in major bleeding (relative risk, 1.32 [CI, 0.73 to 2.37]). Anticoagulant prophylaxis had no effect on all-cause mortality (relative risk, 0.97 [CI, 0.79 to 1.19]).

Limitations: 2 of 9 included studies were not double-blind.

Conclusions: Anticoagulant prophylaxis is effective in preventing symptomatic venous thromboembolism during anticoagulant prophylaxis in at-risk hospitalized medical patients. Additional research is needed to determine the risk for venous thromboembolism in these patients after prophylaxis has been stopped.

Ann Intern Med. 2007;146:278-288. www.annals.org

For author affiliations, see end of text.

Prevention of venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep venous thrombosis (DVT), is an important management issue in at-risk hospitalized medical patients. The Agency for Healthcare Research and Quality ranks prevention of VTE as the first priority out of 79 preventive initiatives that can improve patient safety in health care settings (1). Anticoagulant prophylaxis with unfractionated heparin or low-molecular-weight heparin has been described as an efficacious, safe, and cost-effective intervention to prevent DVT in medical patients (2–4). Furthermore, the American College of Chest Physicians Guidelines on Antithrombotic Therapy gives anticoagulant prophylaxis in medical patients a grade 1A recommendation (4).

Despite these considerations, anticoagulant prophylaxis in at-risk hospitalized medical patients is administered to only 16% to 33% of such patients (5–7), whereas up to 90% of at-risk surgical patients receive prophylaxis (8, 9). One reason that may explain this apparent under utilization of anticoagulant prophylaxis in medical patients is a lack of evidence that such treatment prevents clinically important outcomes, such as PE, which has been shown in surgical patients (10). Individual randomized trials of anticoagulant prophylaxis in medical patients have been underpowered to show a reduction in PE and have assessed treatment effects on asymptomatic, venography-detected DVT, which is a less compelling outcome (11–13).

Therefore, we performed a meta-analysis of randomized, controlled trials of anticoagulant prophylaxis in medical patients, focusing on the effects of treatment on clinically important efficacy outcomes (any PE, fatal PE, symptomatic DVT, and all-cause mortality) and safety outcomes (major bleeding). The aim of our study was to determine the effects of treatment while patients were receiving anticoagulant prophylaxis and to assess to what extent, if any, these treatment effects were maintained after prophylaxis had been stopped.

Methods

Data Sources

We attempted to identify all published and unpublished randomized, controlled trials, irrespective of language, that described anticoagulant prophylaxis in medical patients by using MEDLINE (1966 to September 2006, week 3), EMBASE (1980 to September 2006, week 3), and Cochrane Central Register of Controlled Trials (2006, Issue 3) databases. We show the search strategy in the

See also:

Print
Editors' Notes 279

Web-Only
Appendix Table
Appendix Figure
CME quiz
Conversion of figures and tables into slides

Appendix Table (available at www.annals.org). We supplemented the strategy by manually reviewing reference lists and by contacting content experts.

Study Selection

Two reviewers independently performed study selection. Disagreements were resolved through discussion and by a third reviewer. We included a study if it was a randomized, controlled trial that compared treatment with a prophylactic dose of anticoagulant (unfractionated heparin, low-molecular-weight heparin, or fondaparinux) with no treatment (placebo or no intervention) in medical patients. Included studies also had to assess at least 1 of the following outcomes: symptomatic PE, symptomatic DVT, major bleeding, or all-cause mortality. We excluded studies that involved only patients with stroke, as this is a selected, high-risk subgroup (4), or if outcomes were not objectively confirmed.

For trials that were published in more than 1 study, we extracted data from the most recent publication and used earlier publications to clarify data. To assess agreement between reviewers for study selection, we used the kappa statistic, which measures agreement beyond chance (14). A κ value greater than 0.6 is considered substantial agreement, and a κ value greater than 0.8 is considered almost perfect agreement (15).

Study Data Extraction

We extracted and presented data according to the QUORUM criteria (16). For each study, 2 reviewers, who were blinded to the identity of the study authors and journal in which the studies were published, independently extracted data on study design, patient characteristics, and anticoagulant prophylaxis. We extracted data on the following treatment efficacy outcomes: any PE (that is, symptomatic nonfatal and fatal PE), fatal PE, symptomatic DVT, and all-cause mortality. Data were also extracted on major bleeding (safety outcome). We only considered objectively documented and independently adjudicated outcomes. We accepted the reported definitions of major bleeding and did not attempt to reclassify these events. We defined major bleeding as that which required transfusion of 2 or more units of packed red blood cells, involved a critical site (for example, retroperitoneal), or was fatal.

To determine the treatment effects of anticoagulant prophylaxis during the time patients were receiving prophylaxis, we extracted data on efficacy and safety outcomes during the on-treatment period. To determine whether the treatment effects of anticoagulant prophylaxis were maintained after prophylaxis had been stopped, we planned to extract data on efficacy outcomes during the entire on-treatment and after-treatment periods.

If outcome data could not be identified for extraction, we contacted the study authors by e-mail to request these data. If a response was not received after 15 days, we sent a second e-mail and contacted the secondary authors. We resolved disagreements about study data extraction by consensus or by discussion with a third reviewer.

Context

Anticoagulant prophylaxis of venous thromboembolism in hospitalized patients is better established in surgical practice than in medical practice, in part because of the lack of convincing clinical trial evidence in hospitalized medical patients.

Contributions

The authors found 9 controlled, randomized trials of currently recommended unfractionated heparin or low-molecular-weight heparin prophylaxis regimens in hospitalized medical patients. Prophylaxis decreased the rate of pulmonary embolism, including fatal pulmonary emboli, by one half—a statistically significant reduction. Prophylaxis did not change other outcomes, including major bleeding.

Caution

Methods to identify good candidates for prophylaxis do not yet exist.

Implications

Anticoagulant prophylaxis substantially reduces the risk for venous thromboembolism in hospitalized medical patients.

—The Editors

Anticoagulant Regimens

We assessed the following anticoagulant regimens that are currently recommended for the prevention of VTE: unfractionated heparin, 5000 IU 2 or 3 times daily; enoxaparin, 40 mg or 60 mg once daily; enoxaparin, 30 mg twice daily; nadroparin, 4000 IU or 6000 IU once daily; dalteparin, 5000 IU once daily; and fondaparinux, 2.5 mg once daily. We excluded anticoagulant regimens that are not recommended for clinical use (for example, enoxaparin, 20 mg once daily).

Study Quality Assessment

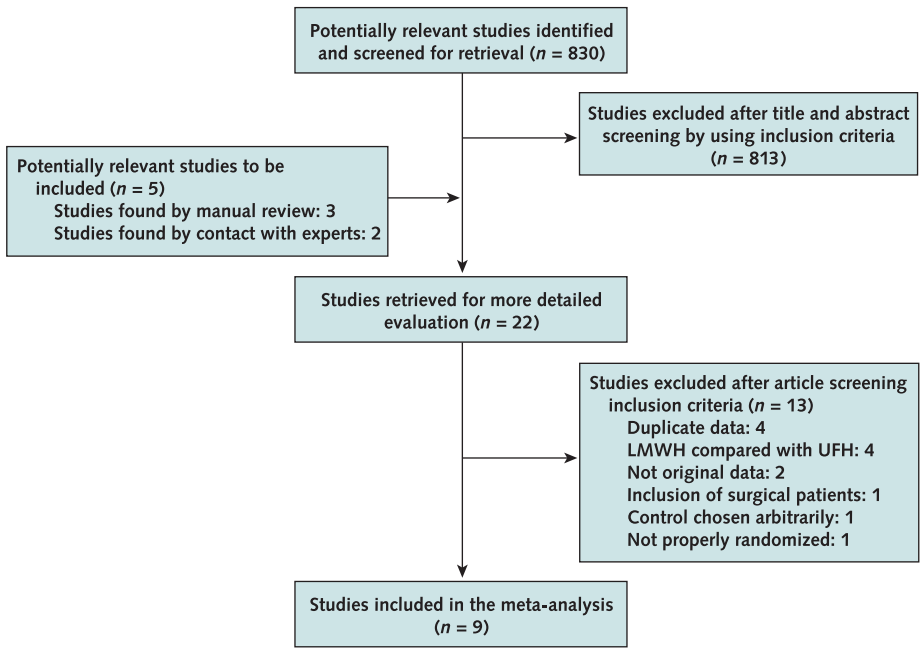
Two reviewers who were blinded to the identity of the study authors and the journals in which the studies were published independently assessed study quality. The reviewers evaluated study quality by considering methods used to generate the randomization sequence, methods of double-blinding, and the description of patient withdrawals and dropouts.

Data Synthesis and Analyses

Primary Analyses

We determined pooled relative risks and 95% CIs for any symptomatic PE (which included fatal and nonfatal PE), fatal PE, symptomatic DVT, all-cause mortality, and major bleeding in patients who received anticoagulant prophylaxis or no prophylaxis. We planned separate analyses for treatment effects during prophylaxis and for treatment effects after prophylaxis had been stopped. For treatment

Figure 1. **Identification of eligible studies.**



LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

effects that were statistically significant, we determined the absolute risk reduction and number-needed-to-treat for benefit (NNT_B) to prevent an outcome. We pooled data by using the Mantel–Haenszel method (17), and we performed a fixed-effects model by using Review Manager, version 4.2.8 (RevMan, Cochrane Collaboration, Oxford, England). Because combining trials with extremely low or zero event rates can yield biased results, we repeated the analyses using StatXact software, version 7 (Cytel Software Corporation, Cambridge, Massachusetts), which provides exact fixed-effect point and interval estimates for the odds ratio (18). The appropriateness of pooling data across studies was assessed using the I^2 test for heterogeneity, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error (19).

Sensitivity Analyses

We repeated sensitivity analyses by using only studies that satisfied each item of our prespecified quality evaluation (20). We created funnel plots of effect size versus standard error to assess for publication bias (21).

Role of the Funding Source

We received no financial support for this review.

RESULTS

Study Identification and Selection

We identified 830 potentially relevant studies from the following databases: 382 from MEDLINE, 358 from EMBASE, and 375 from the Cochrane Library (**Figure 1**). We excluded 813 studies after screening their title and abstract by using the predefined inclusion and exclusion criteria and retrieved the remaining 17 studies for more detailed evaluation (22–38). We identified another 3 studies by manual review of references of retrieved articles (39–41). Through contact with content experts, we identified 2 other studies (42, 43). Of the 22 retrieved studies, 13 were excluded for the following reasons: 4 because they had duplicate data (24, 29, 31, 34); 4 because they did not have an untreated control group (25, 27, 30, 36); 2 because they did not contain original data (26, 28); 1 because it included medical and surgical patients (37); 1 because it was not properly randomized (40); and 1 because it identified the control group arbitrarily and not by randomization (39). Therefore, we included 9 studies in our systematic review (22, 23, 32, 33, 35, 38, 41–43). We had excellent interobserver agreement for study selection (κ = 0.98). **Table 1** shows the characteristics of the included studies.

Study Quality

In **Table 1**, we show that random allocation of treatment was adequate in 9 studies, 7 studies were reported as double-blind, 5 studies provided a description of patient withdrawals, and 7 studies had concealed treatment allocation. Outcomes were systematically documented in all studies but 1 (35), in which episodes of nonfatal PE were not documented in a systematic manner. No studies included a run-in period; 1 study was a pilot performed to assess the feasibility of a larger randomized trial (43).

Outcomes

We summarize outcomes assessed during anticoagulant prophylaxis in **Table 2**. Although we performed an analysis of efficacy and safety of prophylaxis after treatment was stopped, we decided not to present these findings because of concerns about their validity. Furthermore, a single study by Gardlund and colleagues (35) contribute to more than 80% of all fatal PE outcomes that occurred after prophylaxis was stopped. Although not presented, we did perform an analysis of efficacy and safety of prophylaxis after treatment was stopped and its results did not vary substantially from those we present during the on-treatment period.

Primary Analyses

Any Pulmonary Embolism

In 9 studies (22, 23, 32, 33, 35, 38, 41–43) that assessed any PE during anticoagulant prophylaxis, the outcome occurred in 20 of 9915 (0.20%) patients who received prophylaxis and in 49 of 10 043 (0.49%) patients who received no prophylaxis (**Figure 2**). Anticoagulant prophylaxis was associated with a significant reduction in PE (relative risk, 0.43 [CI, 0.26 to 0.71]; absolute risk reduction, 0.29%; NNT_B, 345).

Fatal Pulmonary Embolism

In 7 studies (22, 23, 32, 33, 35, 41, 42) that assessed fatal PE during anticoagulant prophylaxis, the outcome occurred in 14 of 9687 (0.14%) patients who received prophylaxis and in 39 of 9823 (0.39%) patients who received no prophylaxis (**Figure 3**). Anticoagulant prophylaxis was associated with a statistically significant reduction in fatal PE (relative risk, 0.38 [CI, 0.21 to 0.69]; absolute risk reduction, 0.25%; NNT_B, 400).

Symptomatic Deep Venous Thrombosis

In 4 studies (23, 33, 42, 43) that assessed DVT during anticoagulant prophylaxis, the outcome occurred in 10 of 2619 (0.38%) patients who received prophylaxis and in 21 of 2587 (0.81%) patients who received no prophylaxis (**Figure 4**). Anticoagulant prophylaxis was associated with a nonsignificant reduction in symptomatic DVT (risk ratio, 0.47 [CI, 0.22 to 1.00]).

All-Cause Mortality

In 5 studies (22, 23, 32, 33, 41) that assessed all-cause mortality during anticoagulant prophylaxis, death occurred in 158 of 3676 (4.3%) patients who received prophylaxis and in 165 of 3679 (4.5%) patients who received no prophylaxis (**Figure 5**). No apparent reduction in all-cause mortality occurred with anticoagulant prophylaxis (relative risk, 0.97 [CI, 0.77 to 1.21]).

Major Bleeding

In 8 studies (22, 23, 32, 33, 38, 41–43) that assessed major bleeding during prophylaxis, the outcome occurred in 25 of 4301 (0.58%) patients who received prophylaxis and in 19 of 4304 (0.44%) patients who received no prophylaxis (**Figure 6**). Anticoagulant prophylaxis was associated with a nonsignificant increase in major bleeding (relative risk, 1.32 [CI, 0.73 to 2.37]). We found no heterogeneity for this outcome across studies (I^2 = 29.7%).

Heterogeneity

Except for major bleeding, we found no heterogeneity across studies for all outcomes assessed (I^2 = 0%).

Sensitivity Analysis

We confirmed the results of the primary analyses by using sensitivity analyses that considered only double-blind studies. Adequate allocation concealment and description of withdrawals and dropouts did not change the results of the primary analyses. Similarly, repeating our analyses with StatExact software did not change the results of the primary analyses.

Publication Bias

As shown in the **Appendix Figure** (available at www.annals.org), we assessed publication bias by using funnel plots for 2 outcomes: any PE and major bleeding. We did not have enough studies to create a funnel plot for the other outcomes. The funnel plot for any PE was asymmetrical, with an absence of studies in the bottom right side of the plot. This suggests that we did not include small studies that demonstrated that prophylaxis is associated with an increased risk for PE and all-cause mortality. The funnel plot for major bleeding appeared symmetrical, suggesting the absence of publication bias.

Discussion

The principal finding from this study is that anticoagulant prophylaxis decreases the risk for symptomatic nonfatal and fatal VTE in hospitalized medical patients who are at risk for VTE. Anticoagulant prophylaxis reduced the relative risk for symptomatic PE during treatment by 58%. Similarly, anticoagulant prophylaxis reduced the relative risk that patients would develop fatal PE during treatment by 64%. Finally, anticoagulant prophylaxis reduced the risk for symptomatic DVT by 53% (CI, 22% to 100%). Anticoagulant prophylaxis had no effect on all-cause mortality, probably because of the large number of deaths due to any cause that were unrelated to VTE compared with the small number of deaths that were attributed to PE.

Our findings are relevant to numerous hospitalized medical patients, many of whom are at risk for VTE and may be eligible to receive anticoagulant prophylaxis (44). Consequently, clinicians should apply our findings to clinical practice with caution and should consider anticoagulant prophylaxis within the context of absolute therapeutic benefits, potential harms, and costs as well as the potential limitations of our findings.

Table 1. **Study Characteristics and Study Quality Assessment***

Study, Year (Reference)	Indication for Prophylaxis	Patient Exclusion Criteria	Anticoagulant Prophylaxis Regimen	Patients, *n*
Belch et al., 1981 (38)	Heart failure, chest infection	Age <40 or >80 y, iodine allergy, high risk for bleeding, DVT or PE on admission, bed rest for more than 2 d before admission	Unfractionated heparin, 5000 U 3 times daily	100
Dahan et al., 1986 (41)	Congestive heart failure (NYHA III–IV), acute or respiratory infectious disease	Age <65 y, ongoing anticoagulant or antiplatelet therapy, active bleeding, coagulation disorder, predicted short hospitalization, thyroid disease, iodine allergy, autopsy not available if necessary	Enoxaparin, 60 mg once daily	270
Gardlund et al., 1996 (35)	Infectious disease	Age <55 y, ongoing anticoagulant treatment, readmission within 60 d of randomization, active bleeding, coagulation disorder, dialysis, liver failure, HIV infection, terminal disease, data not available	Unfractionated heparin, 5000 U twice daily	11 693
Samama et al., 1999 (33)	Congestive heart failure (NYHA III–IV), acute or chronic respiratory disease, acute infectious or rheumatologic disease	Age <40 y, pregnant or breast-feeding women, women of childbearing age not using contraception, stroke or major surgery in previous 3 mo, contraindication to contrast dye, thrombophilia, creatinine level >150 μmol/L (>1.7 mg/dL), intubation, HIV infection, uncontrolled hypertension (>200/120 mm Hg), active peptic ulcer disease, bacterial endocarditis, conditions associated with an increased risk for bleeding, hypersensitivity to heparin or HIT, platelets 100 × 10^9/L, prolonged aPTT, INR >1.2, ongoing (>48 h) or required anticoagulant therapy	Enoxaparin, 40 mg once daily	1102
Fraisse et al., 2000 (32)	Acute decompensated chronic obstructive pulmonary disease with mechanical ventilation	Age <40 or >80 y, weight <45 or >110 kg, history of DVT in previous 6 mo or DVT at inclusion, organic lesion that could bleed, severe liver failure (aPTT <50%), creatinine level >300 μmol/L (>3.4 mg/dL), uncontrolled hypertension (DBP >120 mm Hg), congenital or acquired coagulation disorder, hypersensitivity to heparins, previous HIT, anticoagulants or contraindication to angiography, ongoing anticoagulant or antiplatelet therapy	Nadroparin, 3800–5700 U once daily	223
Leizorovicz et al., 2004 (23)	Congestive heart failure (NYHA III–IV), acute or chronic respiratory disease, infectious and rheumatologic disease	Age <40 y, >3 d of immobility, acute coronary syndrome within 1 mo, major surgical or invasive procedure in previous mo or planned in next 2 wk, bacterial endocarditis, immobilized lower limb, stroke within 3 mo, high risk for bleeding, platelets <100 × 10^9/L, thromboprophylaxis given for >48 h before randomization, contraindication to heparin, serum creatinine level >177 μmol/L (>2.0 mg/dL), hepatic insufficiency or active hepatitis, pregnancy or breast-feeding, life expectancy <1 mo	Dalteparin, 5000 U once daily	3706
Mahé et al., 2005 (22)	Congestive heart failure (NYHA III–IV), acute or respiratory disease, nonpulmonary sepsis, cancer	Age <40 y, uncontrolled hypertension (SBP >240 mm Hg and DBP >120 mm Hg), active gastroduodenal ulcer, serum creatinine level >300 μmol/L (>3.4 mg/dL), prothrombin time <50%, platelets <50 × 10^9/L, conditions requiring anticoagulation, stroke or major surgery within 30 d and anticoagulation or antiplatelet therapy in previous 7 d, pregnancy	Nadroparin, 7500 U once daily	2472
Lederle et al., 2006 (43)	Hospitalization in general medical unit	Age <60 y, uncontrolled hypertension (SBP >220 mm Hg and DBP >110 mm Hg), platelets <100 × 10^9/L, occurrence within the last 30 d of myocardial infarction, stroke, major surgery (defined as requiring general spinal or epidural anesthesia and lasting >30 minutes), any eye surgery, current use or contraindication to anticoagulation	Enoxaparin, 4000 U once daily	280
Cohen et al., 2006 (42)	Congestive heart failure (NYHA III–IV), acute respiratory, infectious, or inflammatory disease	Age <60 y; high risk for bleeding; acute bacterial endocarditis; cerebral metastasis; recent stroke; brain, spinal, or ophthalmologic surgery; indwelling intrathecal or epidural catheter; creatinine level >180 μmol/L (>2.04 mg/dL); hypersensitivity to contrast dye; anticipated intubation for >24 h; antithrombotic use within 48 h before randomization; indication for anticoagulant prophylaxis or therapy; life expectancy <1 mo	Fondaparinux, 2.5 mg once daily	849

* aPTT = activated partial thromboplastin time; DBP = diastolic blood pressure; DVT = deep venous thrombosis; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; NYHA = New York Heart Association; PE = pulmonary embolism; SBP = systolic blood pressure.
† An autopsy was performed in 123 of 252 patients who died.
‡ Except for deaths, events were limited to those recorded during initial and subsequent hospitalizations.

Table 1—**Continued**

Follow-up Duration, *d*	Outcomes Assessed	Funding Source	Concealed Treatment Allocation	Double-Blind	Description of Withdrawals
14	PE, major bleeding during hospitalization	Not declared	No	No	No
10	Death, PE, and major bleeding during hospitalization	Not declared	Not defined	Yes	Yes
60	Fatal PE during hospitalization, death and PE after a follow-up period	Karolinska Institute, Stockholm, Sweden; Dalarna Research Institute, Falun, Sweden; Trygg Hansa Research Foundation, Stockholm, Sweden; and Lowens Lakemedel AB, Malmo, Sweden	Yes	No	Yes
110	Death, PE, DVT, and major bleeding during hospitalization and after a follow-up period	Rhone-Poulenc Rorer, Collegeville, Pennsylvania	Yes	Yes	Yes
11	Death, PE, and major bleeding during hospitalization	Sanofi, Paris, France	Yes	Yes	No
90	Death, PE, DVT, and major bleeding during hospitalization and after a follow-up period	Pharmacia Corporation, Peapack, New Jersey	Yes	Yes	No
21	Death, fatal PE, and major bleeding during hospitalization†	Independent Research from Sanofi-Choay, Paris, France	Yes	Yes	Yes
90	PE, DVT, and major bleeding complication during hospitalization and after a follow-up period‡; death after a follow-up period	Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development, Washington, DC	Yes	Yes	Yes
32	Death, PE, DVT, and major bleeding during hospitalization and after a follow-up period	Sanofi-Synthelabo, Paris, France, and NV Organon, Oss, the Netherlands, sponsored the study and carried out on-site monitoring of all participants	Yes	Yes	No

Table 2. **Outcomes Examined (Total Number of Events per Total Number of Study Participants) during the Period When the Intervention Group Received Anticoagulant Prophylaxis***

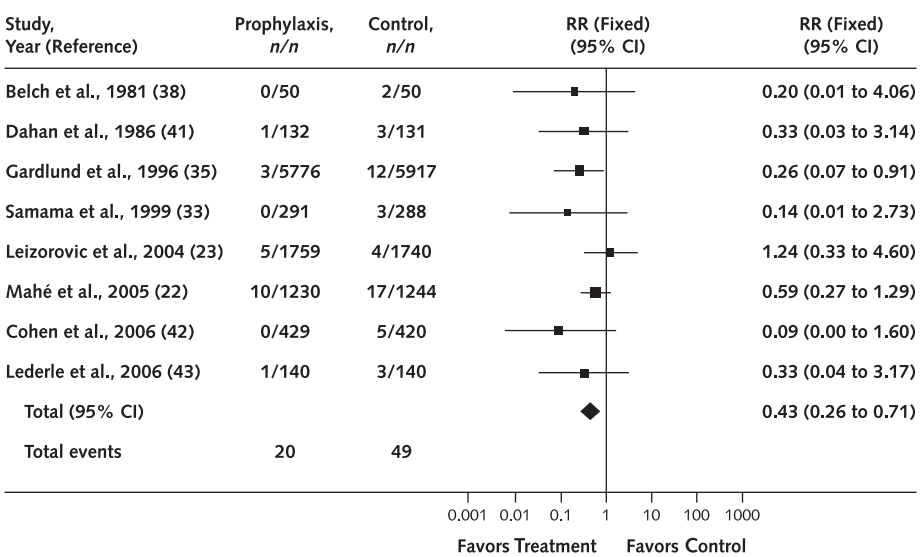
Author, Year (Reference)	Outcomes during Anticoagulant Prophylaxis				
	PE, *n/n (%)*	Fatal PE, *n/n (%)*	Symptomatic DVT, *n/n (%)*	Death, *n/n (%)*	Major Bleeding, *n/n (%)*
Belch et al., 1981 (38)	2/100 (2)	–	–	–	0/100 (0)
Dahan et al., 1986 (41)	4/262 (1.5)	4/262 (1.5)	–	12/263 (4.6)	4/263 (1.5)
Gardlund et al., 1996 (35)	15/11 693 (0.13)	15/11 693 (0.13)	–	–	–
Samama et al., 1999 (33)	3/579 (0.52)	0/579 (0)	3/579 (0.52)	28/720 (3.9)	10/372 (2.7)
Fraisse et al., 2000 (32)	0/221 (0)	0/221 (0)	–	16/221 (7.2)	9/211 (4.3)
Leizorovicz et al., 2004 (23)	9/3499 (0.26)	2/3636 (0.05)	16/3498 (0.46)	15/3677 (0.41)	8/3706 (0.22)
Mahé et al., 2005 (22)	27/2474 (1.09)	27/2474 (1.09)	–	252/2474 (10.19)	4/2744 (1.46)
Lederle et al., 2006 (43)	4/280 (1.43)	–	12/280 (4.29)	–	7/280 (2.5)
Cohen et al., 2006 (42)	5/849 (0.59)	5/624 (0.80)	–	–	2/839 (0.24)

* DVT = deep venous thrombosis; PE = pulmonary embolism.

The absolute risk reductions for PE and fatal PE during anticoagulant prophylaxis are modest (0.29% and 0.25%, respectively). Thus, 345 hospitalized medical patients at risk for VTE would need to be treated with anticoagulant prophylaxis to prevent 1 symptomatic PE, and 400 patients would need to be treated to prevent 1 death due to PE. Potential harms of anticoagulant prophylaxis include a nonsignificant 32% relative risk increase (0.14% absolute risk increase) for major bleeding. Anticoagulant prophylaxis may also confer an increased risk for heparin-induced thrombocytopenia. This adverse effect was not routinely assessed in the studies we reviewed but has been reported to occur in 1.4% of medical patients who receive unfractionated heparin as anticoagulant prophylaxis (45). The risk for heparin-induced thrombocytopenia in medical patients who receive low-molecular-weight heparin is not known, but based on comparisons in surgical patients, the risk is probably less than that of unfractionated heparin (46). The potential costs of administering anticoagulant prophylaxis to at-risk medical patients are substantial, with approximately 7 million medical patients hospitalized annually in the United States (44). To our knowledge, no studies have assessed the cost-effectiveness of anticoagulant prophylaxis to prevent symptomatic VTE in hospitalized patients (3, 47, 48).

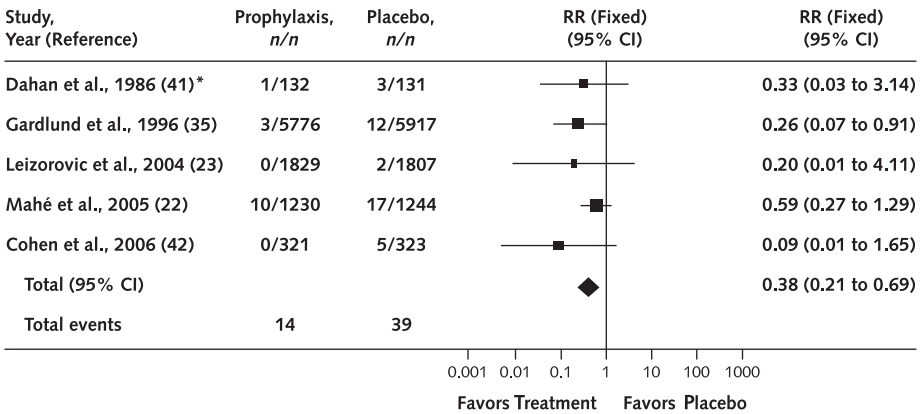
Limitations of our meta-analysis may affect the validity of our findings. First, because not all trials used a double-blind design, a lower threshold for diagnostic testing in patients who did not receive anticoagulant prophylaxis (diagnostic suspicion bias) might exist, with the potential that more symptomatic outcomes were detected in untreated patients enrolled in the unblinded trials. However, given the clinical consequences of missed and untreated VTE, the development of clinical features compatible with VTE

Figure 2. **Any pulmonary embolism during anticoagulant prophylaxis.**



RR = relative risk.

Figure 3. **Fatal pulmonary embolism during anticoagulant prophylaxis.**

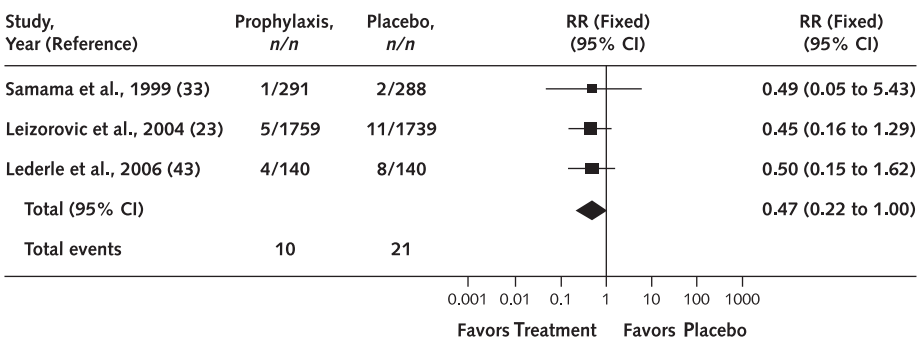


RR = relative risk.
*One patient in the prophylaxis group died of myocardial infarction, but autopsy also revealed a pulmonary embolism. Therefore, the patient was included as having a fatal pulmonary embolism.

in at-risk medical patients might trigger diagnostic testing irrespective of whether anticoagulant prophylaxis was administered. Nonetheless, we cannot exclude the potential for overdetection of outcomes in patients who did not receive prophylaxis. Second, our finding of an asymmetrical funnel plot (**Appendix Figure**, available at www.annals.org) for the outcome of PE suggests that there may have been unpublished studies in which anticoagulant prophylaxis increased the risk for PE. However, after excluding 3 studies with small sample sizes (bottom left of the plot), the risk reduction for PE remained unchanged (relative risk, 0.44 [CI, 0.24 to 0.79]). The validity of our findings is supported by our sensitivity analysis, which was consistent with our findings from all pooled studies and was limited to high-quality trials, in which the treatment effects of anticoagulant prophylaxis remained. Third, we acknowledge that our pool of studies for the outcomes of fatal PE and DVT was small (5 or fewer) and caution is required in interpreting findings pertaining to these outcomes.

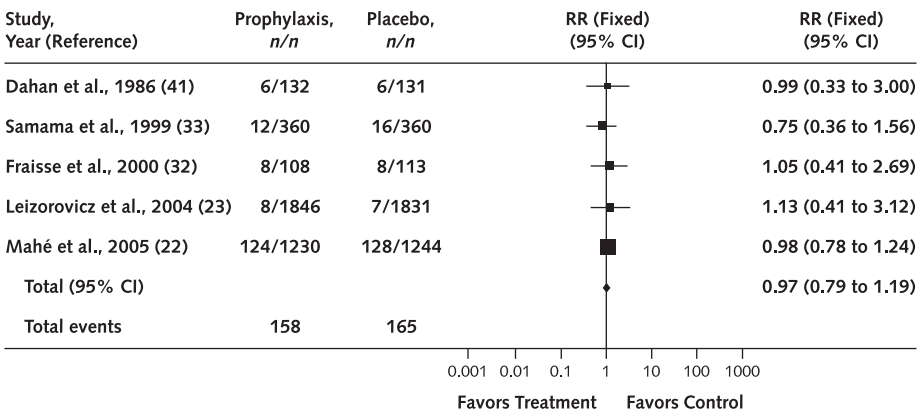
Other potential limitations include the lack of head-to-head comparisons of different anticoagulants. Consequently, we cannot compare the relative efficacy of 1 drug over another drug or low-molecular-weight heparins with unfractionated heparin (30, 36). Our findings pertain to the effects of anticoagulant prophylaxis as a drug class. In addition, at least 5 of the 9 included studies were supported by pharmaceutical companies. However, because researchers maintained adequate allocation concealment in almost all studies and because we only considered outcomes evaluated in an objective manner, the funding sources for the studies probably did not systematically affect the results. Finally, because no standardized definition for major bleeding in medical patients has been adopted in clinical trials of antithrombotic treatments, the definition for major bleeding varied across studies (49). This should not affect our comparisons of bleeding in treated and nontreated patients but will affect estimates of absolute bleeding rates.

Figure 4. **Symptomatic deep venous thrombosis during anticoagulant prophylaxis.**



RR = relative risk.

Figure 5. **All-cause mortality during anticoagulant prophylaxis.**

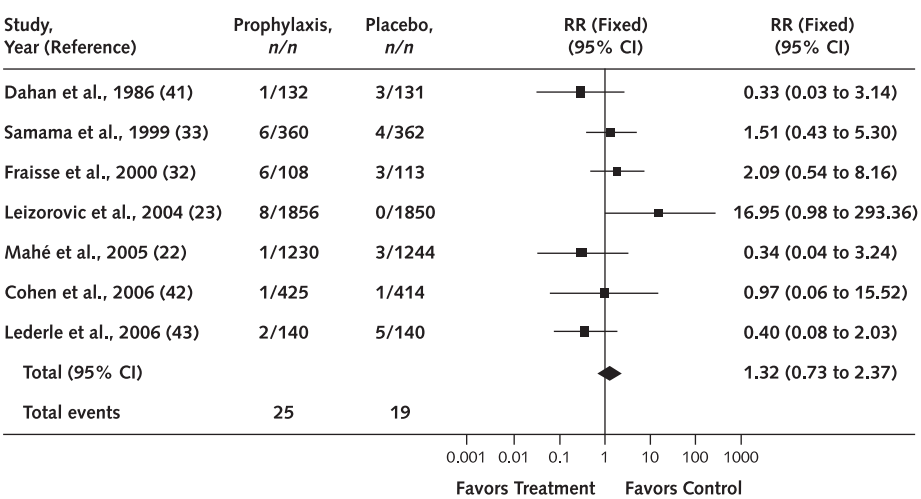


RR = relative risk.

Our findings should be interpreted by considering the totality of evidence that anticoagulant prophylaxis prevents clinically important VTE, the limitations of our study and the potential harms and costs of treatment. On balance, we believe that the observed magnitude of risk reduction and the consistency of findings across outcomes analyzed in our study support the use of anticoagulant prophylaxis in at-risk medical patients. These findings may be attenuated, but are unlikely to be rendered null, by the aforementioned limitations of this meta-analysis.

Clinicians applying these findings to hospitalized medical patients are faced with 2 practical questions: Who should receive anticoagulant prophylaxis and for how long? The first question is problematic because, unlike surgical patients in whom risk for VTE is largely determined by the type of surgery (4), medical patients comprise a spectrum of risk for VTE. Furthermore, because anticoagulant prophylaxis has potential harms, increases health care costs, and is associated with modest treatment benefits in terms of absolute risk reduction, its use should be selective and perhaps limited to higher-risk patients. Clinicians may consider prophylaxis in immobile patients and those with congestive heart failure, respiratory disease, active cancer, previous VTE, sepsis, or acute inflammatory disease (4, 50–52). However, there is no established risk-classification scheme that identifies patient groups in which risk for VTE is sufficiently high to warrant prophylaxis or to identify lower-risk groups in which prophylaxis can be safely avoided. Further research is needed to clarify these important issues. The optimal duration of treatment in patients who do receive prophylaxis is uncertain. We originally planned to determine the effects of treatment while pa-

Figure 6. **Major bleeding during anticoagulant prophylaxis.**



RR = relative risks.

tients were receiving anticoagulant prophylaxis and during the period after prophylaxis had been stopped. However, we decided not to include the latter analyses because of substantive methodological problems with data from that period. Therefore, until further research is done to address this issue, we cannot comment on the effect of anticoagulant prophylaxis on the risk for VTE after treatment is stopped.

In summary, anticoagulant prophylaxis is effective in preventing symptomatic nonfatal and fatal VTE in at-risk hospitalized medical patients. The risk for VTE in patients after prophylaxis is stopped remains to be clarified and should be evaluated in future studies.

From McMaster University and St. Joseph's Healthcare, Hamilton, Ontario, Canada.

Acknowledgments: The authors thank Dr. Qilong Yi for his helpful review of and contribution to the manuscript.

Grant Support: Dr. Crowther is a Career Investigator of the Heart and Stroke Foundation of Ontario. Dr. Lim holds a Mentorship award from the Canadian Institutes of Health Research.

Potential Financial Conflicts of Interest: *Consultancies:* J.D. Douketis (Agen Biomedical), M.A. Crowther (Sanofi-Aventis, Pfizer Inc., Leo Laboratories, GlaxoSmithKline, Organon, Artisian Therapeutics); *Honoraria:* J.D. Douketis (Sanofi-Aventis, Pfizer Inc., Leo Pharma), M.A. Crowther (Sanofi-Aventis, Pfizer Inc., Leo Laboratories, GlaxoSmithKline, Organon Artisian Therapeutics); *Grants received:* M.A. Crowther (Sanofi-Aventis, Pfizer Inc., Leo Laboratories, GlaxoSmithKline, Organon, Artisian Therapeutics).

Requests for Single Reprints: James D. Douketis, MD, St. Joseph's Hospital, Room F-544, 50 Charlton Avenue East, Hamilton L8N 4A6, Ontario, Canada; e-mail, jdouket@mcmaster.ca.

Current author addresses are available at www.annals.org.

References

1. **Shojania KG, Duncan BW, McDonald KM, Wachter RM, eds.** Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment no. 43. Rockville, MD: Agency for Healthcare Research and Quality; 2001. AHRQ publication 01-E058. Accessed at www.ahrq.gov/clinic/ptsafety/ on 8 October 2006.

2. **Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmüller A, Juillard-Delsart D, et al.** Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost. 2000;83:14-9. [PMID: 10669147]

3. **de Lissovoy G, Subedi P.** Economic evaluation of enoxaparin as prophylaxis against venous thromboembolism in seriously ill medical patients: a US perspective. Am J Manag Care. 2002;8:1082-8. [PMID: 12500884]

4. **Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S-400S. [PMID: 15383478]

5. **Goldhaber SZ, Dunn K, MacDougall RC.** New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. Chest. 2000;118:1680-4. [PMID: 11115458]

6. **Stratton MA, Anderson FA, Bussey HI, Caprini J, Comerota A, Haines ST, et al.** Prevention of venous thromboembolism: adherence to the 1995 American College of Chest Physicians consensus guidelines for surgical patients. Arch Intern Med. 2000;160:334-40. [PMID: 10668835]

7. **Kahn SR, Panju A, Geerts A, Pineo GF, Desjardins L, Turpie AGG, et al.** Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. Thromb Res. 2007;119:145-55. Epub 3 March 2006. [PMID: 16516275]

8. **Caprini JA, Arcelus J, Sehgal LR, Cohen EB, Reyna JJ.** The use of low molecular weight heparins for the prevention of postoperative venous thromboembolism in general surgery. A survey of practice in the United States. Int Angiol. 2002;21:78-85. [PMID: 11941278]

9. **Mesko JW, Brand RA, Iorio R, Gradisar I, Heekin R, Leighton R, et al.** Venous thromboembolic disease management patterns in total hip arthroplasty and total knee arthroplasty patients: a survey of the AAHKS membership. J Arthroplasty. 2001;16:679-88. [PMID: 11547365]

10. **Collins R, Scrimgeour A, Yusuf S, Peto R.** Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318:1162-73. [PMID: 3283548]

11. **Gallus AS, Nurmohammed M, Kearon C, Prins M.** Thromboprophylaxis in non-surgical patients: who, when and how? Haemostasis. 1998;28 Suppl 3:71-82. [PMID: 10069765]

12. **Lowe GD, Sandercock PA, Rosendaal FR.** Prevention of venous thromboembolism after major orthopaedic surgery: is fondaparinux an advance? Lancet. 2003;362:504-5. [PMID: 12932379]

13. **Lederle FA.** Heparin prophylaxis for medical patients? [Editorial]. Ann Intern Med. 1998;128:768-70. [PMID: 9556472]

14. **McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R.** Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). CMAJ. 2004;171:1369-73. [PMID: 15557592]

15. **Maclure M, Willett WC.** Misinterpretation and misuse of the kappa statistic. Am J Epidemiol. 1987;126:161-9. [PMID: 3300279]

16. **Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF.** Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999; 354:1896-900. [PMID: 10584742]

17. **Mantel N, Haenszel W.** Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719-48. [PMID: 13655060]

18. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351-75. [PMID: 15116347]

19. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]

20. **Jüni P, Witschi A, Bloch R, Egger M.** The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282:1054-60. [PMID: 10493204]

21. **Sterne JA, Egger M, Smith GD.** Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ. 2001;323:101-5. [PMID: 11451790]

22. **Mahé I, Bergmann JF, d'Azémar P, Vaissie JJ, Caulin C.** Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. Eur J Clin Pharmacol. 2005;61:347-51. [PMID: 15981008]

23. **Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ.** Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110: 874-9. [PMID: 15289368]

24. **Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al.** Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med. 2004;164: 963-8. [PMID: 15136304]

25. **Bergmann JF, Neuhart E.** A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. Thromb Haemost. 1996;76: 529-34. [PMID: 8902991]

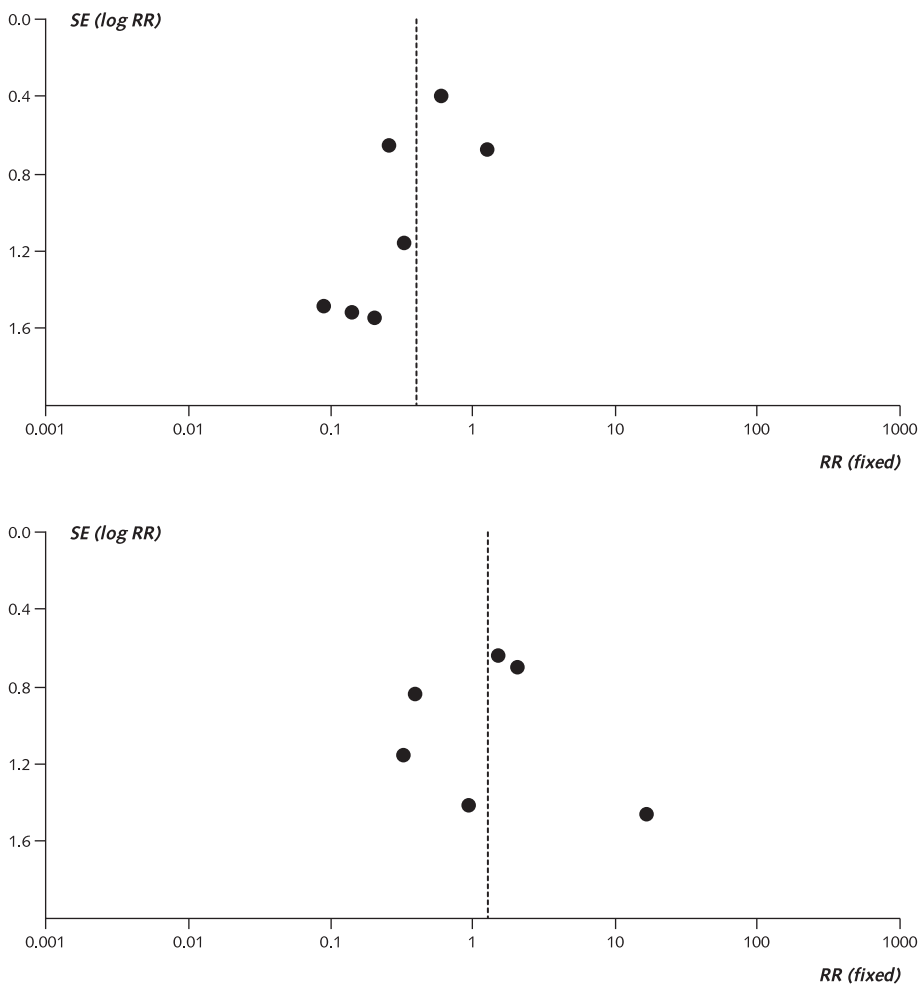
26. **Allen TW.** Low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. J Am Osteopath Assoc. 1996;96:335.

27. **Lechler E, Schramm W, Flosbach CW.** The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-

molecular-weight heparin (enoxaparin). The Prime Study Group. Haemostasis. 1996;26 Suppl 2:49-56. [PMID: 8707167]
28. **Pirone F, Tartaglione G, Melaragno E.** [Heparin prophylaxis of deep venous thrombosis and pulmonary embolism in medical patients]. Clin Ter. 1988;126: 267-71. [PMID: 2974396]
29. **Desjardins L, Bara L, Boutitie F, Samama MM, Cohen AT, Combe S, et al.** Correlation of plasma coagulation parameters with thromboprophylaxis, patient characteristics, and outcome in the MEDENOX study. Arch Pathol Lab Med. 2004;128:519-26. [PMID: 15086284]
30. **Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW.** Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J. 2003;145:614-21. [PMID: 12679756]
31. **Vaitkus PT, Leizorovicz A, Goldhaber SZ.** Rationale and design of a clinical trial of a low-molecular-weight heparin in preventing clinically important venous thromboembolism in medical patients: the prospective evaluation of dalteparin efficacy for prevention of venous thromboembolism in immobilized patients trial (the PREVENT study). Vasc Med. 2002;7:269-73. [PMID: 12710842]
32. **Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, et al.** Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Am J Respir Crit Care Med. 2000;161:1109-14. [PMID: 10764298]
33. **Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al.** A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341:793-800. [PMID: 10477777]
34. **Bergmann JF, Caulin C.** Heparin prophylaxis in bedridden patients [Letter]. Lancet. 1996;348:205-6. [PMID: 8684189]
35. **Gärdlund B.** Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. Lancet. 1996;347:1357-61. [PMID: 8637340]
36. **Harenberg J, Roebruck P, Heene DL.** Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. Haemostasis. 1996;26:127-39. [PMID: 8738587]
37. **Cade JF.** High risk of the critically ill for venous thromboembolism. Crit Care Med. 1982;10:448-50. [PMID: 7044682]
38. **Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR.** Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J. 1981;26:115-7. [PMID: 7291971]
39. **Ibarra-Pérez C, Lau-Cortés E, Colmenero-Zubiate S, Arévila-Ceballos N, Fong JH, Sánchez-Martínez R, et al.** Prevalence and prevention of deep venous thrombosis of the lower extremities in high-risk pulmonary patients. Angiology. 1988;39:505-13. [PMID: 3377270]
40. **Halkin H, Goldberg J, Modan M, Modan B.** Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med. 1982;96:561-5. [PMID: 7073148]
41. **Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al.** Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis. 1986;16: 159-64. [PMID: 3710294]
42. **Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al.** Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ. 2006;332:325-9. [PMID: 16439370]
43. **Lederle FA, Sacks JM, Fiore L, Landefeld CS, Steinberg N, Peters RW, et al.** The prophylaxis of medical patients for thromboembolism pilot study. Am J Med. 2006;119:54-9. [PMID: 16431185]
44. **Graves EJ, Gillum BS.** Detailed diagnoses and procedures, National Hospital Discharge Survey, 1994. Vital Health Stat 13. 1997:1-145. [PMID: 9090313]
45. **Girolami B, Prandoni P, Stefani PM, Tanduo C, Sabbion P, Eichler P, et al.** The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. Blood. 2003;101:2955-9. [PMID: 12480713]
46. **Martel N, Lee J, Wells PS.** Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106:2710-5. [PMID: 15985543]
47. **Lamy A, Wang X, Kent R, Smith KM, Gafni A.** Economic evaluation of the MEDENOX trial: a Canadian perspective. Medical Patients with Enoxaparin. Can Respir J. 2002;9:169-77. [PMID: 12068338]
48. **Nuijten MJ, Berto P, Kosa J, Nadipelli V, Cimminiello C, Spreafico A.** Cost-effectiveness of enoxaparin as thromboprophylaxis in acutelly ill medical patients from the Italian NHS perspective. Recenti Prog Med. 2002;93:80-91. [PMID: 11887350]
49. **Schulman S, Kearon C.** Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692-4. [PMID: 15842354]
50. **Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al.** Risk factors for venous Thromboembolism in hospitalized patients with acute medical illness. Arch Intern Med 2004;164:963-8.
51. **Labarere J, Bosson JL, Brion JP, Fabre M, Imbert B, Carpentier P, et al.** Validation of a clinical guideline on prevention of venous thromboembolism in medical inpatients: a before-and-after study with systematic ultrasound examination. J Intern Med. 2004;256:338-48. [PMID: 15367177]
52. **Samama MM.** An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000;160:3415-20. [PMID: 11112234]

Current Author Addresses: Drs. Dentali and Gianni: Inusbria University, Viale Borri 57, 21100 Varese, Italy.
Drs. Douketis, Lim, and Crowther: McMaster University, 50 Charleton Avenue East, Hamilton L8N 4A6, Ontario, Canada.

Appendix Figure. **Funnel plot of studies for outcome of symptomatic pulmonary embolism (*top*) and major bleeding (*bottom*).**



RR = relative risk; SE = standard error.

Appendix Table. Literature Search Strategy*

1 Venous Thrombosis/pc, ep [Prevention & Control, Epidemiology] (2971)
2 Pulmonary Embolism/pc, ep [Prevention & Control, Epidemiology] (4127)
3 or/1-2 (6463)
4 Heparin/ (40289)
5 low molecular weight heparin.mp. or exp Heparin, Low-Molecular-Weight/ (7802)
6 dalteparin$.mp. or exp Tedelparin/ (734)
7 (tedelparin$ or fragmin$ or kabi2165 or kabi 2165 or k2165 or k 2165 or fr860 or fr 860).mp. (360)
8 enoxaparin$.mp. or exp ENOXAPARIN/ (1888)
9 (lovenox or clexane or klexane or pk10169 or pk 10169 or emt996 or emt 996 or emt967 or emt 967).mp. (172)
10 nadroparin$.mp. or exp NADROPARIN/ (407)
11 (fraxiparin$ or seleparin$ or tedegliparin$ or cy216 or cy 216).mp. (285)
12 tinzaparin$.mp. (202)
13 (innohep or logiparin$).mp. (54)
14 (ardeparin$ or normiflo or rd11885 or rd 11885).mp. (36)
15 (bemiparin$ or hibor or ivor or zibor or badyket).mp. (157)
16 (certoparin$ or alpharin$ or sandoparin$ or troparin$ or embolex or monoembolex).mp. (87)
17 (parnaparin$ or fluxum or op2123 or op 2123 or minidalton or alphaLMWH or alpha LMWH).mp. (33)
18 (reviparin$ or lu473111 or lu 473111 or clivarin$).mp. (122)
19 fondaparinux.mp. (404)
20 arixtra.mp. (36)
21 antixarin.mp. (1)
22 or/4-21 (45973)
23 3 and 22 (2008)
24 limit 23 to clinical trial (382)

* Database: Ovid MEDLINE <1966 to September week 3 2006>.