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Prevention of VTE in Nonsurgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **This guideline addressed VTE prevention in hospitalized medical patients, outpatients with cancer, the chronically immobilized, long-distance travelers, and those with asymptomatic thrombophilia.**
Methods: **This guideline follows methods described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**
Results: **For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B) and suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B). For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B). For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) or intermittent pneumatic compression (IPC) (Grade 2C). For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis (Grade 2C). For critically ill patients who are bleeding or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 2C). In outpatients with cancer who have no additional risk factors for VTE we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommend against the prophylactic use of vitamin K antagonists (Grade 1B).**
Conclusions: **Decisions regarding prophylaxis in nonsurgical patients should be made after consideration of risk factors for both thrombosis and bleeding, clinical context, and patients' values and preferences.**
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Abbreviations: APLA = antiphospholipid antibodies; ASA = acetylsalicylic acid; CVC = central venous catheter; GCS = graduated compression stockings; HIT = heparin-induced thrombocytopenia; HR = hazard ratio; INR = international normalized ratio; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RAM = risk assessment model; RCT = randomized controlled trial; RR = risk ratio; SCLC = small cell lung cancer; UFH = unfractionated heparin; VFP = venous foot pump; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B)**.**

Remarks: In choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance, and ease of administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs (eg, prices of various pharmacologic agents in individual hospital formularies).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B)**.**

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, we recommend against anticoagulant thromboprophylaxis (Grade 1B)**.**

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) **or intermittent pneumatic compression (IPC)** (Grade 2C)**, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2B)**.**

Remarks: Patients who are particularly averse to the potential for skin complications, cost, and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis.

2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)**.**

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C)**.**

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C)**.**

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding, we suggest mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C) **until the bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2C)**.**

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against

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routine prophylaxis with LMWH or LDUH (Grade 2B) **and recommend against the prophylactic use of vitamin K antagonists** (Grade 1B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B)**.**

Remarks: Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling central venous catheters, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and suggest against the prophylactic use of vitamin K antagonists** (Grade 2C)**.**

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C)**.**

6.1.1. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C)**.**

6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle during travel (Grade 2C)**. For all other long-distance travelers, we suggest against the use of GCS** (Grade 2C)**.**

6.1.3. For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C)**.**

7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)**.**

This article focuses on prevention of VTE in nonsurgical populations. Because they are addressed in other chapters in these guidelines,[1,2] we do not include prevention of VTE in patients with trauma and spinal cord injury and in patients with ischemic and hemorrhagic stroke.

Adverse consequences of unprevented VTE include symptomatic DVT and pulmonary embolism (PE), fatal PE, chronic postthrombotic syndrome, and increased risk of recurrent VTE. We consider the desirable and undesirable consequences of antithrombotic prophylaxis to prevent VTE in the following populations/patient groups: (1) hospitalized acutely ill medical patients, (2) critically ill patients, (3) patients with cancer receiving cancer treatment in the outpatient setting, (4) patients with cancer with indwelling central venous catheters (CVCs), (5) Chronically immobilized patients, (6) long-distance travelers, and (7) asymptomatic persons with thrombophilia. We also consider the use of statins (HMG-CoA reductase inhibitors) to prevent VTE. Table 1 describes the question definition (population, intervention, comparator, and outcome) and eligibility criteria for studies considered in each section of this article.

1.0 Methods

The methodology of these guidelines follows the general approach of Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.[3] In brief, panel members conducted literature searches to update the existing evidence base, seeking systematic reviews and trials published since the previous iteration of the guidelines, and rated the quality of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation framework. The panel considered the balance of benefits and harm, patients' values and preferences, and patients' context and resources to develop weak or strong recommendations. In this article, we identified three areas with sparse high-quality evidence: (1) the benefits of prophylaxis as measured by reduction of the incidence of symptomatic VTE events, (2) resource use and cost-effectiveness, and (3) the benefits of screening strategies for VTE in nonsurgical patients.

1.1 Outcomes of Interest

We selected similar patient-important outcomes across recommendations. These include symptomatic DVT, PE, death from PE, major bleeding, heparin-induced thrombocytopenia (HIT), and mechanical thromboprophylaxis complications (when applicable). In addition, for patients with CVCs, we include catheter failure as an outcome.

As the mortal outcome of greatest interest, when data were available, we have chosen treatment-related mortality (PE deaths, hemorrhagic deaths). For pharmacologic interventions, when available, we provide data on fatal bleeding and fatal intracranial

Table 1—*[Introduction] Structured Clinical Questions*

Population	Intervention(s)	Comparator	Outcome	Methodology
Hospitalized acutely ill medical patients	Mechanical prophylaxis (GCS, IPC, IVC filter) and/or pharmacologic prophylaxis (ASA, LDUH, LMWH, fondaparinux, VKA, oral DTI, oral direct Xa inhibitors)	No treatment, placebo, mechanical prophylaxis, and/or pharmacologic prophylaxis	Symptomatic DVT and PE, death, major bleeding events, mechanical prophylaxis complications	RCTs
	LDUH bid	LDUH tid		
	Extended-duration pharmacologic prophylaxis, after initial short-duration prophylaxis	Short-duration prophylaxis		
	Any screening for asymptomatic VTE with ultrasound	No screening		
All patients admitted to a critical care unit	Routine screening with ultrasound for asymptomatic VTE	No screening	Symptomatic DVT, PE, death, major bleeding events	RCTs and observational studies
	LMWH, LDUH	No treatment, placebo, mechanical prophylaxis, and/or pharmacologic prophylaxis	Symptomatic DVT and PE, death, major bleeding events, mechanical prophylaxis complications	RCTs and observational studies
Patients with cancer				
Receiving cancer treatment in outpatient setting	Mechanical prophylaxis (GCS) and/or pharmacologic prophylaxis (ASA, LDUH, LMWH, fondaparinux, VKA, oral DTI, oral direct Xa inhibitors)	No treatment, placebo, mechanical prophylaxis, and/or pharmacologic prophylaxis	Symptomatic DVT and PE, death, major bleeding events, mechanical prophylaxis complications	RCTs and observational studies
With indwelling central venous catheters	Pharmacologic prophylaxis (ASA, LDUH, LMWH, fondaparinux, VKA, oral DTI, oral direct Xa inhibitors)	No treatment, placebo, or pharmacologic prophylaxis	Symptomatic DVT and PE, death, major bleeding events, catheter failure	RCTs and observational studies
Chronically immobilized patients (e.g. nursing home or rehab residents, immobilized persons living at home)	Mechanical prophylaxis (GCS) and/or pharmacologic prophylaxis (ASA, LDUH, LMWH, fondaparinux, VKA, oral DTI, oral direct Xa inhibitors)	No treatment, placebo, mechanical prophylaxis, and/or pharmacologic prophylaxis	Symptomatic DVT and PE, death, major bleeding events, mechanical prophylaxis complications	RCTs and observational studies
Long-distance travelers	GCS, LMWH, ASA	No treatment, placebo, mechanical prophylaxis, and/or pharmacologic prophylaxis	Symptomatic DVT, PE, death, major bleeding events	RCTs and observational studies
All patients	Prognostic factors associated with risk of VTE	N/A	Symptomatic DVT and PE, death from PE	RCTs and observational studies
All patients	Prognostic factors associated with risk of bleeding	N/A	Major bleeding events, death from bleeding	RCTs and observational studies
Asymptomatic persons with thrombophilia (inherited thrombophilia, LAC, APLA)	Mechanical prophylaxis (GCS) and/or pharmacologic prophylaxis (ASA, LDUH, LMWH, VKA)	No treatment or placebo	Symptomatic DVT, PE, death, major bleeding events	RCTs and observational studies
Asymptomatic persons (ie, no previous VTE)	Statins	No treatment or placebo	Symptomatic DVT, PE, death	RCTs and observational studies

For tradeoff of benefits and harms, only symptomatic VTE events are considered. APLA = antiphospholipid antibodies; ASA = acetylsalicylic acid; DTI = direct thrombin inhibitor; GCS = graduated compression stockings; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LAC = lupus anticoagulant; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; VKA = vitamin K antagonist.

bleeding as a subset of all-cause mortality, and for the outcome of major bleeding, when available, we provide data on intracranial bleeding and GI bleeding (the most common type of "critical organ" bleeding expected in nonsurgical populations). Given that anticoagulants used to prevent VTE are administered for short periods of time, major bleeding and fatal bleeding are likely to be rare events, except during critical illness.

1.2 Values and Preferences

Little is known about the distribution of patients' values and preferences in the context of VTE prevention in nonsurgical settings. In developing the recommendations for this guideline, panelists made estimates of patients' values and preferences often using indirect data from other settings (eg, values and preferences that pertain to anticoagulation in atrial fibrillation).

In our populations, the weights (relative importance) given to the harmful effects (disutilities) of the most representative types of critical organ bleeding, namely GI or, less commonly, intracranial bleeding, will greatly impact the tradeoff between desirable and undesirable consequences of antithrombotic therapy. There are limited data to guide us with respect to the relative impact of VTE events vs bleeding events on patient-perceived state of health; available evidence suggests values and preferences for treatments and for health states vary appreciably between individuals.[4]

In a values rating exercise, Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines panelists used a "feeling thermometer" with anchors at 0 (representing death) and 100 (representing full health) to rate patient scenarios for various clinical outcomes in terms of the value placed on a year in which the events depicted in the scenario occurred.[3] Median ratings were similar for the outcomes of symptomatic DVT, PE, and catheter thrombosis (80, 75, and 80, respectively) and severe GI bleeding (75), whereas the median rating for intracranial bleeding (stroke scenario) was 40. Therefore, we used 1:1 ratio of symptomatic VTE to major extracranial bleeding and 2.5:1 ratio of symptomatic VTE to intracranial bleeding for tradeoffs.

We considered that preventative and screening recommendations require higher-quality evidence supporting benefit than therapy recommendations. This decision is a value-based judgment. In making our recommendations, when there is uncertain benefit and an appreciable probability of important harm or patient burden associated with treatment, we recommend against such treatments.

1.3 Estimating Baseline Risk

In making clinical recommendations, guideline developers need to consider the balance of benefits and harms in terms of absolute treatment effect on patient-important symptomatic events in addition to relative measures of risk. The panelists of the four articles dealing with VTE prevention faced challenges in finding these data and developed several possible approaches for estimating the effect of prophylaxis on the incidence of symptomatic VTE events. In this article, we used two different approaches for hospitalized patients in non-critical care settings and for critically ill patients, based on the availability of data.

1.3.1 Baseline Risk in Hospitalized Medical Patients: Since medical patients have a significantly heterogeneous risk for VTE, the guideline panel sought to evaluate preventive strategies in two different strata of patients (low risk and high risk). We decided against simply using as the baseline estimate the pooled average risk of DVT (0.8%) and PE (0.4%) reported in the control arms of the randomized controlled trials (RCTs) of thromboprophylaxis in hospitalized medical patients, as it is evident from the trials' eligibility criteria that patients with heterogeneous risk were enrolled (Table S1) (Tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available online. See the "Acknowledgments" for more information.). Also, there is uncertainty about the generalizability of trial results to other populations, as in many of the trials the ratio of patients screened to patients enrolled was very high (eg, ≥ 100), and probable underestimation of absolute numbers of symptomatic events, as patients diagnosed with asymptomatic DVT via trial-mandated screening tests are typically treated with anticoagulants. Incidence estimates from most observational studies were unsatisfactory because they were not stratified by the use of thromboprophylaxis and were also reported in very heterogenous populations (Table S2).

To estimate baseline risk for patients with low and high VTE risk, we used data from risk assessment models (RAMs). Several RAMs have been proposed for use in hospitalized medical patients (Table S3).[5-7] Limitations of most RAMs include lack of prospective validation, applicability only to high-risk subgroups, inadequate follow-up time, and excessive complexity.

In a prospective observational study of 1,180 inpatients, a predefined RAM (Padua Prediction Score, modified after Kucher[8]) assigned points to 11 common VTE risk factors (Table 2)[9] and categorized hospitalized medical patients as low risk (< 4 points; 60.3% of patients) or high risk (≥ 4 points; 39.7% of patients) for VTE. Attending physicians were not notified of their patients' risk categories. Patients were followed for symptomatic VTE for 90 days. VTE occurred in 11.0% of high-risk patients who did not receive prophylaxis vs 0.3% of low-risk patients, a > 30-fold difference in risk (hazard ratio [HR], 32.0; 95% CI, 4.1-251.0). Among 711 low-risk patients, two (0.3%) developed VTE (1 PE, 1 PE with DVT). Among 283 high-risk patients who did not receive prophylaxis, the risk of DVT was 6.7%, nonfatal PE 3.9%, and fatal PE 0.4%. Hence, for baseline risk for low- and high-risk strata, we used risk estimates provided by the Padua Prediction Score.[9] Despite the limitations of this risk model (small number of events, suboptimal

Table 2—*Risk Factors for VTE in Hospitalized Medical Patients*[9]

Risk Factor	Points
Active cancer[a]	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility[b]	3
Already known thrombophilic condition[c]	3
Recent (≤ 1 mo) trauma and/or surgery	2
Elderly age (≥ 70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

In the Padua Prediction Score risk assessment model, high risk of VTE is defined by a cumulative score ≥ 4 points. In a prospective observational study of 1,180 medical inpatients, 60.3% of patients were low risk and 39.7% were high risk. Among patients who did not receive prophylaxis, VTE occurred in 11.0% of high-risk patients vs 0.3% of low-risk patients (HR, 32.0; 95% CI, 4.1-251.0). Among high-risk patients, the risk of DVT was 6.7%, nonfatal PE 3.9%, and fatal PE 0.4%.[9] HR = hazard ratio.

[a]Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 mo.

[b]Anticipated bed rest with bathroom privileges (either because of patient's limitations or on physician's order) for at least 3 d.

[c]Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

validation), this model provides the best available basis for judging hospitalized patients' risk.

We considered a number of options for baseline risk of major bleeding. We considered bleeding events reported in the Padua prediction score study. However, this study stratified bleeding events according to thrombosis risk, not bleeding risk (1 of 283 in the low VTE risk group [0.4%; 95% CI, 0.0-2.0] and 1 of 711 in the high VTE risk group [0.1%; 95% CI, 0.0-0.8]).[9] We also considered bleeding events in a large observational study by Decousus[10]; however, this study did not report bleeding according to use of pharmacoprophylaxis. Therefore, we chose to use 0.4% (19 of 4,304) derived from the control arm of trials of thromboprophylaxis in medical patients as the estimate of baseline risk of major bleeding (section 2.1). Where possible, we presented data on intracranial bleeding separately from major bleeding events.

1.3.2 Baseline Risk in Critically Ill Patients: Critical care trials have routinely screened patients for asymptomatic DVT, which are usually promptly treated if detected. Hence, an accurate estimate of risk of symptomatic DVT is not available from trials of critically ill patients receiving no prophylaxis, and PE events are generally rare. We used two approaches to estimate the baseline risk and absolute risk difference in critically ill patients. When symptomatic events were reported, such as DVT in the trials by Shorr et al[11] and in PROTECT,[12] we used these data directly to estimate the baseline risk, relative risk (RR), and risk difference. When symptomatic events were not reported in the trials, such as the PE outcome in trials that compared unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) vs placebo, we opted to use a baseline risk derived from symptomatic PEs reported in three observational studies.[13-15] The risk ratio (RR) was derived from the trials in which events were likely a mix of symptomatic and asymptomatic events. The former approach has the advantage of directness but may suffer from imprecision and poor applicability. The latter approach requires imputations that make the evidence indirect.

2.0. Hospitalized Acutely Ill Medical Patients

2.1 Risk Factors for VTE in Hospitalized Medical Patients

Hospitalization for acute medical illness is associated with an eightfold increased risk of VTE[16] and accounts for about one-fourth of all VTE events in the community.[17,18] Among hospitalized patients, 50% to 75% of VTE events, including fatal PE, occur in those hospitalized on the medical service.[16,19] Risk factors for VTE in hospitalized medical patients include intrinsic factors, such as increasing age (especially > 70 years), previous VTE, known thrombophilia, and various comorbid illnesses, such as cancer, heart failure, or respiratory failure, and extrinsic factors, such as immobilization for ≥ 3 days and hormonal medications[5,20-22] (Table 2).[9]

2.2 Risk Factors for Bleeding in Hospitalized Medical Patients

A recent multinational observational study reported on risk factors at admission that were independently predictive of in-hospital bleeding (the analysis combined major and nonmajor clinically relevant bleeding) among 10,866 hospitalized medical patients. The strongest risk factors were active gastroduodenal ulcer, bleeding in 3 months before admission, and platelet count $< 50 \times 10^9$/L, followed by age > 85 years, hepatic failure, severe renal failure, and ICU or critical care unit admission (Table 3).[10] Although data on incidence of bleeding were not provided separately by use vs nonuse of prophylaxis (overall rate of major bleeding was 0.76%), the above variables remained predictive of bleeding when the model was adjusted for pharmacologic prophylaxis. A bleeding risk score that included these and additional variables was developed by the authors, who reported that more than one-half of all major bleeding episodes occurred in the 10% of hospitalized medical patients who had a bleeding risk score ≥ 7.0.

Although this risk score is complex and has not yet been validated, the panel considered patients to have an excessive risk of bleeding if they had multiple risk factors or had one of the three risk factors with

Table 3—*Independent Risk Factors for Bleeding in 10,866 Hospitalized Medical Patient*[10]

Risk Factor[a]	Total Patients, No. (%) (N = 10,866)	OR (95% CI)
Active gastroduodenal ulcer	236 (2.2)	4.15 (2.21-7.77)
Bleeding in 3 mo before admission	231 (2.2)	3.64 (2.21-5.99)
Platelet count $< 50 \times 10^9$/L	179 (1.7)	3.37 (1.84-6.18)
Age ≥ 85 y (vs < 40 y)	1,178 (10.8)	2.96 (1.43-6.15)
Hepatic failure (INR > 1.5)	219 (2.0)	2.18 (1.10-4.33)
Severe renal failure (GFR < 30 mL/min/m^2)	1,084 (11.0)	2.14 (1.44-3.20)
ICU or CCU admission	923 (8.5)	2.10 (1.42-3.10)
Central venous catheter	820 (7.5)	1.85 (1.18-2.90)
Rheumatic disease	740 (6.8)	1.78 (1.09-2.89)
Current cancer	1,166 (10.7)	1.78 (1.20-2.63)
Male sex	5,367 (49.4)	1.48 (1.10-1.99)

Data shown were obtained by multiple logistic regression analysis for characteristics at admission independently associated with in-hospital bleeding (major bleeding and clinically relevant nonmajor bleeding combined). GFR = glomerular filtration rate; INR = international normalized ratio.
[a]Although not specifically studied in medical patients, one would also expect dual antiplatelet therapy to increase the risk of bleeding.

the strongest association with bleeding (OR > 3.0): active gastroduodenal ulcer, bleeding in 3 months before admission, and platelet count $< 50 \times 10^9$/L.

2.3 Any Anticoagulant vs None to Prevent VTE

We used data from three contemporary, high-quality systematic reviews to assess the benefits and harms of anticoagulant prophylaxis vs no prophylaxis in hospitalized, acutely ill medical patients.[23-25] In general, the trials included acutely ill hospitalized patients (typically, the mean age of enrolled patients was > 65 years) admitted for congestive heart failure, severe respiratory disease, or acute infectious, rheumatic, or inflammatory conditions, who were immobilized and had one or more additional VTE risk factors including but not limited to age > 40 years, active cancer, previous VTE, or serious infection (Table S2). Prophylactic anticoagulant regimens included low-dose unfractionated heparin (LDUH) tid, LDUH bid, various LMWHs, and fondaparinux. Duration of use of prophylaxis ranged from 6-21 days or discharge from hospital, whichever came first. In all trials, routine screening for DVT was performed.

Meta-analysis of these trials demonstrates that anticoagulant thromboprophylaxis is associated with significant reduction in fatal PEs (RR, 0.41; 95% CI, 0.22-0.76; two fewer per 1,000 [95% CI, from one fewer to three fewer]). When we apply the relative effect of anticoagulant thromboprophylaxis obtained from these meta-analyses to baseline risks obtained from risk assessment models, we find that thromboprophylaxis is associated with a reduction in symptomatic DVT (RR, 0.47; 95% CI, 0.22-1; one fewer per 1,000 [95% CI, from one fewer to 0 fewer] in low-risk patients; 34 fewer per 1,000 [95% CI, from 51 fewer to 0 fewer] in high-risk patients). The effect on nonfatal PE, major bleeding, and all-cause mortality was not statistically significant and is described in terms of relative and absolute effects (Table 4, Table S4). No trial reported the incidence of HIT.

Based on these data, the panel judged that moderate-quality evidence suggests that thromboprophylaxis is effective in reducing symptomatic DVT and fatal PE in acutely ill, hospitalized, immobilized medical patients who have characteristics similar to those enrolled in the above RCTs, and moderate-quality evidence suggests a modest relative and very small absolute increase in bleeding risk. Based on the above RCTs, the panel considered that providing prophylaxis for 6 to 21 days, until full mobility is restored or until discharge from hospital, whichever comes first, is a reasonable approach. The recommendation to prophylax applies only to the higher-risk patients (Table 2). In low-risk patients, VTE is too infrequent to warrant prophylaxis.

Table 4—*[Section 2.3] Summary of Findings: Should Anticoagulant Prophylaxis (LMWH, UFH, Fondaparinux) vs Placebo/No Treatment Be Used in Hospitalized Medical Patients?*[24-26]

Outcomes	Anticipated Absolute Effects		Relative Effect (95% CI)	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)
	Baseline Risk[a]	Risk Difference With Anticoagulant Prophylaxis (95% CI)			
Symptomatic DVT	Low risk		RR, 0.47 (0.22-1)	5,206 (4 RCTs) 1-14 d	Moderate due to imprecision[b]
	2 per 1,000	1 fewer per 1,000 (from 1 fewer to 0 more)			
	High risk				
	67 per 1,000	34 fewer per 1,000 (from 51 fewer to 0 more)			
Nonfatal pulmonary embolism	Low risk		RR, 0.61 (0.23-1.67)	5,206 (6 RCTs) 1-22 d	Moderate due to imprecision[b]
	2 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 more)			
	High risk				
	39 per 1,000	15 fewer per 1,000 (from 30 fewer to 26 more)			
Major bleeding	4 per 1,000	1 more per 1,000 (from 1 fewer to 6 more)	OR, 1.32 (0.73-2.37)	8,605 (8 RCTs) 10-110 d	Moderate due to imprecision[b]
Overall mortality	45 per 1,000	1 fewer per 1,000 (from 9 fewer to 8 more)	OR, 0.97 (0.79-1.19)	7,355 (5 RCTs) 1-22 d	Moderate due to imprecision[b]
Thrombocytopenia	13 per 1,000	1 fewer per 1,000 (from 6 fewer to 7 more)	OR, 0.91 (0.54-1.53)	4,624 (3 RCTs) 6-21 d	Low due to risk of bias and imprecision[b]

GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio; UFH = unfractionated heparin. See Table 1 legend for expansion of other abbreviations.

[a]Baseline risk for DVT and PE in low-risk population were derived from the RAM by Barbar et al.[9] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al).[24]

[b]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.

2.4 LDUH vs LMWH to Prevent VTE

LDUH and LMWH (enoxaparin, nadroparin, or certoparin) have been directly compared in five RCTs.[26-30] Eligibility criteria for RCTs of LDUH vs LMWH in hospitalized medical patients were similar to trials of any anticoagulant vs none to prevent VTE and are shown in Table S5. In all trials, routine screening for DVT was performed. Dosing of LDUH was tid in four trials and bid in one trial.[26]

Pooled results failed to exclude benefit or harm for LMWH vs LDUH for the outcomes DVT (RR, 0.77; 95% CI, 0.50-1.19), PE (RR, 1.00; 95% CI, 0.28-3.59), overall mortality (RR, 0.89; 95% CI, 0.65-1.23), and HIT (RR, 0.50; 95% CI, 0.05-5.48) (Table 5, Table S6). Pooled results for major bleeding suggest a large relative protective effect of LMWH (RR, 0.48; 95% CI, 0.24-0.99) and small absolute (five fewer; 95% CI, 0-7 fewer) reduction in bleeding events per 1,000 patients treated. Evidence is consistent with a similar effect of LMWH and UFH on reduction in thrombosis in acutely ill hospitalized medical patients (though imprecision is such that effects could, in relative terms, be appreciably greater in one treatment or the other). The potential for less bleeding with LMWH represents a benefit that is small, and it may be very small.

2.5 LDUH bid vs tid to Prevent VTE

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), a registry of 15,156 acutely ill hospitalized medical patients enrolled at 52 hospitals in 12 countries, documented marked variation in practices in dosing frequency of LDUH used to prevent VTE. LDUH was prescribed tid in 54% of patients from the United States compared with bid in 85% of non-US patients.[31]

There have been no head-to-head trials comparing bid vs tid LDUH to prevent VTE in hospitalized medical patients. We conducted a mixed-treatment comparison meta-analysis of 16 RCTs that enrolled hospitalized nonsurgical patients at risk for VTE and compared LDUH bid, LDUH tid, or LMWH to each other or to an inactive control.[32] The RR and 95% credible intervals comparing LDUH tid to LDUH bid for DVT, PE, death, and major bleeding (all were indirect comparisons) 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. Due to a lack of reporting, we could not perform this analysis for the outcome HIT. The low-quality evidence from these indirect comparisons provides no compelling evidence that LDUH tid dosing, compared with bid dosing, reduces VTE or causes more bleeding. A future randomized trial comparing these agents is unlikely, considering the large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small. From a patient preference perspective, twice daily injections are likely to be preferred and better tolerated than thrice daily injections.

Table 5—*[Section 2.4] Summary of Findings: Should Anticoagulant Prophylaxis With LMWH vs UFH be Used in Hospitalized Medical Patients?*[23,171]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With UFH[a]	Risk Difference With LMWH (95% CI)
Symptomatic DVT	5,371 (5 RCTs) 1-28 d	Low due to imprecision[b] and indirectness[c]	RR, 0.77 (0.50-1.19)	3 per 1,000	1 fewer per 1,000 (from 2 fewer to 1 more)
Nonfatal pulmonary embolism	5,386 (5 RCTs) 1-28 d	Low due to imprecision[b] and indirectness[c]	RR, 1.00 (0.28-3.59)	2 per 1,000	0 fewer per 1,000 (from 1 fewer to 5 more)
Major bleeding	5,597 (5 RCTs) 1-28 d	Moderate due to imprecision[b]	RR, 0.48 (0.24-0.99)	9 per 1,000	5 fewer per 1,000 (from 0 fewer to 7 fewer)
Overall mortality	5,597 (5 RCTs) 1-28 d	Moderate due to imprecision[b]	RR, 0.89 (0.65-1.23)	27 per 1,000	3 fewer per 1,000 (from 10 fewer to 6 more)
Heparin-induced thrombocytopenia	3,239 (1 RCT) 1-28 d	Low due to risk of imprecision[b] and reporting bias[d]	RR, 0.50 (0.05-5.48)	1 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 more)

See Table 1 and 4 legends for expansion of abbreviations.

[a]Baseline risk is derived from the median control group risk across studies.

[b]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when confidence intervals include appreciable harms and benefits.

[c]The RR used to estimate risk difference included a mix of symptomatic and asymptomatic events, whereas the baseline risk (risk with UFH) was derived from symptomatic events (Riess et al[30]).

[d]Only one study (Riess et al[30]) reported this outcome, suggesting possible reporting bias.

2.6 Anticoagulant Thromboprophylaxis in Acutely Ill Hospitalized Medical Patients From a Resource Perspective

Almost all cost-effectiveness analyses in this population have reported costs per VTE or death averted with the use of anticoagulant prophylaxis, but few studies have reported costs per quality-adjusted life-year gained to compare against preexisting benchmarks. Two studies that reported incremental costs of $65 to $2,534 per quality-adjusted life-year gained over no prophylaxis were both sponsored by the pharmaceutical industry.[33,34] In populations at sufficiently high risk (Tables 2, 6, Table S7), pharmacoprophylaxis is likely to be favorable from a resource standpoint for preventing VTE.[35,36] The comparison between different types of prophylaxis, however, is less clear.

Several studies have suggested that choosing LMWH over LDUH is cost neutral, or even cost saving.[37-41] However, the quality of these analyses is moderate at best. First, many of the authors have had financial disclosures with the pharmaceutical industry, and whether these ties influence the cost-neutral or cost-saving results of LMWH over LDUH is unclear. Second, the performance estimates used in most of these studies have been extracted from the Medical Patients with Enoxaparin (MEDENOX) trial, which did not directly compare LMWH to LDUH[42] and enrolled a very small proportion of patients screened for eligibility, thereby limiting generalizability. Third, although the acquisition costs of LMWH are higher up front (or similar, depending on individual hospital formulary pricing), the eventual cost savings come from treating fewer adverse events—primarily HIT and, possibly, major bleeding—farther downstream. A recent thromboprophylaxis trial in 3,764 critically ill patients reported that the incidence of HIT was 0.3% in patients who received LMWH vs 0.7% in patients who received LDUH;[12] however, a meta-analysis of HIT in patients being treated for acute DVT or PE found no difference in incidence when using LMWH or LDUH.[43] Although the population of this meta-analysis is different from those in the critical care trial; adding the trial data to the meta-analysis does not change its conclusion (RR, 0.71; 95% CI, 0.45-1.11).

In summary, there is no clear evidence in the current literature to support choosing one form of pharmacoprophylaxis over another in the medical population based on outcomes or from a cost-effectiveness standpoint. It would be reasonable to make choices based on patient preference, compliance, and ease of

Table 6—*[Section 2.6] Summary of Findings: Should Aspirin or Other Antiplatelet Drugs Be Used in Hospitalized Medical Patients?*[59]

Outcome	Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk[a]	Risk Difference With Aspirin Prophylaxis (95% CI)
Symptomatic DVT	Imputed data (1 RCT) up to 35 d	Low due to very serious indirectness[b]	RR, 0.71 (0.52-0.97)		Low risk
				2 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 fewer)
					High risk
				67 per 1,000	19 fewer per 1,000 (from 32 fewer to 2 fewer)
Nonfatal pulmonary embolism	Imputed data (64 RCTs) up to 35 d	Low due to very serious indirectness[b]	RR, 0.47 (0.37-0.59)		Low risk
				2 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 fewer)
					High risk
				39 per 1,000	21 fewer per 1,000 (from 25 fewer to 16 fewer)
Major bleeding	Imputed data (1 RCT) up to 35 d	Low due to very serious indirectness[b]	RR, 1.42 (1.16-1.74)	4 per 1,000	2 more per 1,000 (from 1 more to 3 more)
Overall mortality	Imputed data (1 RCT) up to 35 d	Very low due to very serious indirectness[b] and imprecision[c]	RR, 0.97 (0.85-1.10)	45 per 1,000	1 fewer per 1,000 (from 7 fewer to 5 more)

See Table 1 and 4 legends for expansion of abbreviations.

[a]Baseline risk for DVT and PE are derived from the RAM by Barbar et al.[9] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al).[24]

[b]Evidence is indirect because the relative effect is primarily derived from surgical patients (555 of the 26,890 patients included in PEP trial report meta-analysis were high-risk medical patients). DVT and PE baseline risk estimates are derived from a risk assessment model derived in a cohort with a small number of outcome events, hence have uncertainty about them. This uncertainty can be labeled as imprecision or indirectness. Some of the PE events in this meta-analysis may have been fatal.

[c]We will consider the presence of serious imprecision when there are <300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.

administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs.

2.7 Mechanical Methods of Thromboprophylaxis in Hospitalized Medical Patients

Mechanical methods of thromboprophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCs), and venous foot pumps (VFPs). These devices reduce venous stasis, a risk factor for VTE, by displacing blood from the superficial to the deep venous system via the perforating veins, thereby increasing the velocity and volume of flow in the deep system.[44] Most studies of mechanical thromboprophylaxis have been conducted in surgical patients. The primary attraction of mechanical methods is that they do not cause bleeding; hence they may have advantages for patients at risk for VTE who cannot receive anticoagulant-based thromboprophylaxis because they are bleeding or are at risk for bleeding.

2.7.1 Stockings to Prevent VTE: Direct evidence from hospitalized nonsurgical patients is available from three randomized trials that have evaluated the use of thigh-length GCS to prevent VTE in patients with myocardial infarction (one trial)[45] and stroke (two trials)[46,47] (Table 7, Table S8). In pooled analyses, results failed to demonstrate or exclude a beneficial effect on symptomatic DVT or PE. Stocking use increased the risk of skin breaks/ulcers but failed to demonstrate or exclude an effect on lower limb ischemia or amputation. It is not known if hospitalized medical patients have a similar risk of skin complications as hospitalized stroke patients.

In a recent multicenter RCT that compared knee-length to thigh-length GCS to prevent VTE in immobilized patients with acute stroke, proximal DVT

Table 7—*[Section 2.7.1] Summary of Findings: Should Graduated Compression Stockings vs No Stockings Be Used in Hospitalized Medical Patients?*[45,47,48]

Outcome	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk[a]	Risk Difference With Graduated Compression Stockings (95% CI)
Symptomatic DVT	1,256 (1 RCT) 1-30 d	Moderate due to imprecision[b]	RR, 0.91 (0.63-1.29)	Low risk	
				2 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 more)
				High risk	
				67 per 1,000	6 fewer per 1,000 (from 25 fewer to 19 more)
Nonfatal pulmonary embolism	1,256 (1 RCT) 1-30 d	Low due to very serious imprecision[b]	RR, 0.65 (0.33-1.31)	Low risk	
				2 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 more)
				High risk	
				39 per 1,000	14 fewer per 1,000 (from 26 fewer to 12 more)
Overall mortality	1,321 (2 RCTs) 1-30 d	Moderate due to imprecision[b]	RR, 1.06 (0.94-1.20)	45 per 1,000	3 more per 1,000 (from 3 fewer to 9 more)
Skin breaks/ulcers/ blisters/skin necrosis	1,256 (1 RCT) 1-30 d	Very low due to imprecision,[b] indirectness,[c] and methodologic limitations[d]	RR, 4.02 (2.34-6.91)	13 per 1,000	38 more per 1,000 (from 17 more to 75 more)
Lower limb ischemia/ amputation	1,256 (1 RCT) 1-30 d	Very low due to very serious imprecision[b] and methodologic limitations[d]	RR, 3.52 (0.73-16.90)	2 per 1,000	4 more per 1,000 (from 0 fewer to 25 more)

Number of participants is the number of patients who received graduated compression stockings. See Table 1 and 4 legends for expansion of abbreviations.

[a]Baseline risk for DVT and PE are derived from the RAM by Barbar et al.[9] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al[24]). Baseline risk for lower leg ischemia and skin breaks (derived from the control arms of CLOTS trial 1).

[b]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when confidence intervals include appreciable harms and benefits. The exception is for low-risk patients in whom the absolute difference in PE and DVT is fairly small and precise.

[c]Data on skin breaks are from stroke patients.

[d]Assessment of outcomes was based on case-note review and was not blinded to treatment allocation.

(symptomatic or asymptomatic) occurred in 98 of 1,552 (6.3%) patients who received thigh-length stockings vs 138 of 1,562 (8.8%) who received below-knee stockings (RR, 0.71; 95% CI, 0.56-0.92), with no differences between groups in rates of deaths or PE.[48] Skin breaks occurred in 3.9% and 2.9% of patients allocated to thigh-length and knee-length GCS, respectively. These results are difficult to interpret alongside evidence from the CLOTS1 trial that thigh-length GCS were not effective to prevent VTE but suggest that if GCS are used, thigh length is preferred to knee length.[49]

2.7.2 Intermittent Pneumatic Compression Devices to Prevent VTE: An international registry of 15,156 hospitalized acutely ill medical patients found that 22% of US patients received IPC to prevent VTE compared with only 0.2% of patients in other countries.[31] There are no published studies of IPC or VFP devices in hospitalized medical patients. Data are available from a meta-analysis of 22 trials that assessed IPC and VFP, primarily in surgical patients.[50] IPC devices failed to demonstrate or to exclude a beneficial effect on mortality or PE but reduced the risk of DVT (Table 8, Table S9). No data are available on skin complications of IPC use, but one might plausibly expect rates to be similar to those of GCS. The panel considered that the evidence for the different outcomes should be rated down due to indirectness because the RR estimates are derived from surgical populations, in whom effects of IPC may be different than in medical patients, and from a mix of symptomatic and asymptomatic events.

2.7.3 Mechanical Compression vs Heparin: There are no studies that have compared mechanical compression vs anticoagulants to prevent VTE in hospitalized medical patients. Indirect evidence from various orthopedic and nonorthopedic surgical populations was provided in a recent meta-analysis by Eppsteiner of 16 trials (3,887 patients) of various compression modalities tested against LDUH or LMWH.[51] Pooled results for mechanical compression compared with heparin failed to show or to exclude a beneficial or detrimental effect for DVT (RR, 1.07; 95% CI, 0.72-1.61) or PE (RR, 1.03; 95% CI, 0.48-2.22). Mechanical compression was associated with a reduced risk of postoperative bleeding compared with heparin (RR, 0.47; 95% CI 0.31-0.70). The median rate of major bleeding within the study

Table 8—*[Section 2.7.2] Summary of Findings: Should Intermittent Pneumatic Compression Be Used in Hospitalized Nonsurgical Patients With Restricted Mobility?*[25,51,172,173]

Outcome	Source of Data	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk[a]	Risk Difference with IPC (95% CI)
Symptomatic DVT	Imputed data	Moderate due to serious indirectness[b]	RR, 0.43 (0.32-0.58)	Low risk	
				8 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 fewer)
				High risk	
				67 per 1,000	38 fewer per 1,000 (from 46 fewer to 28 fewer)
Nonfatal pulmonary embolism	Imputed data	Low due to indirectness[b] and imprecision[c]	RR, 0.82 (0.41-1.62)	Low risk	
				4 per 1,000	1 fewer per 1,000 (from 1 fewer to 1 more)
				High risk	
				39 per 1,000	7 fewer per 1,000 (from 23 fewer to 24 more)
Overall mortality	Imputed data	Low due to indirectness[b] and imprecision[c]	RR, 1.03 (0.42-2.57)	45 per 1,000	1 more per 1,000 (from 76 fewer to 71 more)
Skin complications	Not reported	...	...	...	...

See Table 1 and 4 legends for expansion of abbreviations.

[a]Baseline risk for DVT and PE are derived from the RAM by Barbar et al.[9] Baseline risk for mortality is derived from the control arm of medical patients in a meta-analysis (Dentali et al[24]).

[b]Serious indirectness is considered because: RR for PE is derived from surgical patients (Roderick et al[50]). RR data are presented for IPC used as monotherapy because this is most relevant to the way IPCs are used in medical patients (ie, in patients who cannot receive anticoagulation). If IPCs are used alone or as adjunct to anticoagulant/antiplatelet therapy, RR is 0.77 (0.41-1.43). This does not change the conclusions of this evidence profile. Another element of indirectness is that DVT in these surgical patients was primarily asymptomatic DVT as ascertained by systematic imaging tests. RR for proximal asymptomatic DVT was similar (0.52; 95% CI, 0.37-0.73). RR data are presented for IPC used as monotherapy because this is most relevant to the way IPCs are used in medical patients (ie, in patients who cannot receive anticoagulation). If IPCs are used alone or as adjunct to anticoagulant/antiplatelet therapy, RR is 0.49 (0.37-0.63). This does not change the conclusions of this evidence profile.

[c]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.

populations was 1.5%, but bleeding rates were not provided by intervention. Subgroup analyses by heparin type suggested that LMWH may reduce risk of DVT compared with compression (RR for compression, 1.80; 95% CI, 1.16-2.79), but remains associated with increased bleeding risk.

2.7.4 Mechanical Compression and Pharmacologic Prophylaxis: Trials in postsurgical patients that compared the combination of intermittent pneumatic compression devices with a pharmacologic method to pharmacologic therapy used alone showed a strong trend toward fewer DVTs with combination therapy (OR, 0.45; 95% CI, 0.20-1.03).[1] Studies that compared the combination of elastic stockings and pharmacologic prophylaxis to pharmacologic therapy alone showed a reduction in symptomatic or asymptomatic DVT (OR, 0.40; 95% CI, 0.25-0.65), but this benefit should be weighed against the increase in skin complications (RR, 4.18; 95% CI, 2.4-7.3) that has been observed in stroke patients treated with elastic compression stockings.[2,3,46]

In summary, indirect data derived primarily from surgical populations suggest that GCS may be modestly effective at preventing asymptomatic DVT and possibly PE in hospitalized medical patients. Direct evidence of low to moderate quality in nonsurgical patients (primarily stroke patients) does not support benefit, and their use in stroke patients is associated with a 5% risk of skin breakdown. IPCs failed to reduce PE in surgical patients but reduced DVT. Of the two methods, GCS has lower cost and greater ease of use and application than IPCs.

Despite the uncertain benefit, mechanical thromboprophylaxis with GCS or IPCs may be preferable to no prophylaxis in patients at appreciable risk for VTE who are also at high risk for bleeding, as the Eppsteiner meta-analysis showed similar effectiveness but reduced rates of bleeding with mechanical compared with heparin prophylaxis among surgical patients.[51] However, as subgroup analysis in that meta-analysis suggested that LMWH may be more effective than compression, and taking into account that the baseline rate of bleeding is lower among medical patients (average from RCTs, 0.4%) than surgical patients, if the bleeding risk is temporary and if patients remain at high risk of VTE (Table 2), pharmacologic thromboprophylaxis should be initiated once the bleeding risk has decreased.

The panel also noted that the use of all mechanical methods of thromboprophylaxis are associated with costs related to purchase and maintenance and the time and vigilance required to ensure optimal compliance. Clinical staff must ensure that the correct size is used, that they are properly applied, and that they are worn at all times. Studies have shown that IPC devices are often not functioning when patients are out of bed or being transported, either due to improperly applied sleeves or nonfunctioning compression pump (not plugged in, power switch not turned on, or air hose compressed). Devices were properly functioning in $<50\%$ of postoperative patients in one study[52] and only 19% of trauma patients in another.[53] Newer battery-powered portable devices are available, and a recent study reported better compliance with these devices than with traditional plug-in devices.[54]

2.8 Extended-Duration Anticoagulant Thromboprophylaxis to Prevent VTE in Hospitalized Medical Patients

Hospitalized medical patients may have risk factors for VTE that persist for weeks to months after hospital discharge. In a medical records review of 1,897 patients diagnosed with VTE in the Worcester, Massachusetts, area, 73.7% of episodes occurred in the outpatient setting; of these, 36.8% occurred in persons hospitalized for medical illness in the preceding 3 months. Among these, two-thirds were diagnosed with VTE within 1 month after hospitalization and one-third between 2 to 3 months after hospitalization.[18] In the MEDENOX RCT in which patients received enoxaparin prophylaxis or placebo for up to 14 days, eight VTE events (8% of the total) occurred between days 15 and 110, of which four were fatal PEs.[42]

Extended-duration thromboprophylaxis refers to prophylaxis that is continued beyond the initial (eg, 5-14 days) course, for up to approximately 35 days total. Evidence from RCTs in hospitalized surgical patients suggests that extended-duration thromboprophylaxis reduces VTE in patients undergoing hip replacement surgery, hip fracture surgery, and surgery for abdominal malignancy.[1,55]

The Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients With Prolonged Immobilization (EXCLAIM) study is the only published RCT of extended duration thromboprophylaxis in hospitalized medical patients.[56] The study population consisted of 6,085 hospitalized patients aged >40 years with acute medical illness (eg, heart failure, respiratory insufficiency, infection) and reduced mobility. All patients received initial open-label enoxaparin (40 mg daily for 10 ± 4 days), and were then randomized to receive extended-duration enoxaparin (40 mg daily for 38 ± 4 days) or placebo. Extended-duration enoxaparin, compared with placebo, reduced the incidence of overall VTE (composite of asymptomatic and symptomatic events) (RR, 0.62; 95% CI, 0.45-0.84) and symptomatic proximal DVT (RR, 0.25; 95% CI, 0.09-0.67) but failed to

exclude benefits or harm for fatal PE (RR, 0.34; 95% CI, 0.01-8.26) and overall mortality (RR, 1.00; 95% CI, 0.7-1.43). The risk of major bleeding was significantly increased with extended-duration enoxaparin (RR, 2.51; 95% CI, 1.21-5.22), and there were four intracranial bleeding events (one fatal) in the extended enoxaparin group compared with none in the placebo group. In terms of absolute effects, extended-duration enoxaparin prevented six fewer symptomatic proximal DVT per 1,000 (95% CI, from three fewer to seven fewer) at a cost of five more major bleeding events per 1,000 (95% CI, from one more to 14 more) (Table 9, Tables S10, S11). In addition to the bleeding risk, extended prophylaxis also entails the burden and cost of daily injection.

2.9 Aspirin or Other Antiplatelet Drugs to Prevent VTE in Hospitalized Medical Patients

The contribution of platelet activation to the pathogenesis of venous thrombosis is less clear than for arterial thrombosis. Although the use of acetylsalicylic acid (ASA) for VTE prevention is appealing because of its low cost, oral administration, and low bleeding rates, the effectiveness of ASA or other antiplatelet drugs to prevent VTE has been studied in relatively few hospitalized medical patients (nine trials, total of 555 patients). These trial data are limited by small numbers of outcome events; reporting of asymptomatic DVT of uncertain clinical relevance, often diagnosed with radiolabeled fibrinogen uptake testing, which has limitations in both sensitivity and specificity; wide variety of antiplatelet drugs studied, including drugs that are no longer in use and that were administered for a mean of 8 weeks; and lack of reporting of rates of bleeding.[57] Among the nine trials, antiplatelet agents were associated with reduced risk of asymptomatic DVT (RR, 0.65; 95% CI, 0.45-0.94) based on 39 of 261 vs 61 of 266 events). Results failed to demonstrate or to exclude a beneficial effect of antiplatelet agents on PE (RR, 0.38; 95% CI, 0.10-1.42) based on three of 275 vs eight of 280 events, respectively. Bleeding rates were not reported.

Our summary of ASA to prevent VTE in hospitalized medical patients (section 2.9) is based on indirect evidence from the PEP (Pulmonary Embolism Prevention) trial, a multicenter trial of ASA 160 mg daily vs placebo for 35 days in hip fracture surgery or elective hip or knee arthroplasty patients[58] for the

Table 9—*[Section 2.8] Summary of Findings: Should Extended-Duration Thromboprophylaxis vs Standard Short-Duration Thromboprophylaxis Be Used for Prevention of VTE in Hospitalized Medical Patients With Reduced Mobility?*[57]

Outcome	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Standard Short-Duration Thromboprophylaxis	Anticipated Absolute Effects: Risk Difference With Extended-Duration Prophylaxis (95% CI)
Symptomatic DVT	4,995 (1 RCT) 24-32 d	Moderate due to methodologic limitations[a]	RR, 0.25 (0.09-0.67)	8 per 1,000	6 fewer per 1,000 (from 3 fewer to 7 fewer)
Nonfatal pulmonary embolism	Not reported	…	…	…	…
Fatal pulmonary embolism	4,995 (1 RCT) 24-32 d	Moderate due to methodologic limitations[a]	RR, 0.34 (0.01-8.26)	1 per 1,000	1 fewer per 1,000 (from 1 fewer to 3 fewer)
Major bleeding	4,995 (1 RCT) 24-32 d	Moderate due to methodologic limitations[a]	RR, 2.51 (1.21-5.22)	3 per 1,000	5 more per 1,000 (from 1 more to 14 more)
Overall mortality	4,995 (1 RCT) 24-32 d	Low due to methodologic limitations[a] and imprecision[b]	RR, 1.00 (0.7-1.43)	22 per 1,000	0 fewer per 1,000 (from 7 fewer to 9 more)
Heparin-induced thrombocytopenia	4,624 (1 RCT) 24-32 d	Very low due to methodologic limitations[a] and very serious imprecision[b]	RR, 3.01 (0.12-73.93)	0 per 1,000	0 more per 1,000 (from 0 fewer to 0 more)

ITT = intention to treat. See Table 1 and 4 legends for expansion of other abbreviations.

[a]Methodologic limitations: change in eligibility criteria part way through the trial and seemed "data-driven"; did not use ITT analysis.

[b]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits. We did not rate down for imprecision in the outcome of fatal PE because the absolute difference was small and precise.

outcomes mortality, symptomatic DVT, and bleeding; and the PEP trial meta-analysis of 53 randomized trials (nine trials conducted in medical patients, as discussed above) of antiplatelet therapy to prevent VTE for the outcome PE. Use of ASA/antiplatelet drugs, compared with placebo, had little or no effect on mortality (RR, 0.97; 95% CI, 0.85-1.10) and was associated with a reduced risk of PE (RR, 0.47; 95% CI, 0.37-0.59), a reduced risk of DVT (RR, 0.71; 95% CI, 0.52-0.97), and an increased risk of nonsurgical site-related bleeding events (RR, 1.42; 95% CI, 1.16-1.74).

The quality of the evidence was rated down for indirectness based on relative effects derived primarily from surgical patients (only 555 of the 26,890 patients included in PEP trial report meta-analysis were high-risk medical patients, and all PEP trials participants were orthopedic surgery patients). The panel judged that based on the low quality of available evidence pertaining to use of ASA to prevent VTE in hospitalized medical patients, no recommendation could be made. There have been no studies of antiplatelet therapy compared with antithrombotic therapy to prevent VTE in acutely ill medical patients.

2.10 Screening for DVT in Hospitalized Medical Patients

Ultrasound screening in medical patients has not been systematically studied. Indirect evidence from hospitalized orthopedic patients[59] and spinal cord injury patients[60] suggests that routine screening is not of benefit to reduce symptomatic VTE events. For example, in a population of patients who had joint arthroplasty and were receiving warfarin prophylaxis, screening compression ultrasonography with subsequent treatment of identified asymptomatic DVT did not reduce the rate of subsequent symptomatic VTE.[59] In a population with a low prevalence of DVT, such as medical patients, even with a highly-specific test such as ultrasound, one would anticipate a substantial number of false-positive results. Moreover, even without considering false-positive results, routine ultrasound screening would be associated with appreciable cost and inconvenience without evidence of benefit.

2.11 Gaps in Care

Low rates of adherence to recommended thromboprophylaxis regimens have been documented worldwide.[31,61-64] In the last few years, research efforts have focused on evaluating strategies to improve uptake of evidence-based VTE prophylaxis regimens in hospitalized patients, including medical patients. Results suggest that passive strategies, such as dissemination of guidelines or educational events, are ineffective. Multicomponent approaches, audit and feedback, and use of automatic reminders, such as preprinted orders, computer alerts, and human alerts, have been shown to be effective strategies; however, VTE prophylaxis continues to be underused or used inappropriately, even with such interventions.[8,64-66]

Recommendations

2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis (Table 2), we recommend anticoagulant thromboprophylaxis with LMWH, LDUH bid, LDUH tid, or fondaparinux (Grade 1B)**.**

Remarks: In choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance, and ease of administration (eg, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs (eg, prices of various pharmacologic agents in individual hospital formularies).

2.4. For acutely ill hospitalized medical patients at low risk of thrombosis (Table 2), we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B)**.**

2.7.1. For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding (Table 3), we recommend against anticoagulant thromboprophylaxis (Grade 1B)**.**

2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with GCS (Grade 2C) **or IPC** (Grade 2C)**, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2B)**.**

Remarks: Patients who are particularly averse to the potential for skin complications, cost, and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis.

2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period

of patient immobilization or acute hospital stay (Grade 2B).

3.0 Critically Ill Patients

3.1 Risk of VTE

The risk of VTE in patients who are admitted to an ICU varies, depending on their acute illness (eg, sepsis), chronic illnesses (eg, congestive heart failure), prehospital diagnoses (eg, prior VTE), and ICU-specific exposures and events (eg, immobilization, surgery, and other invasive procedures [such as central venous catheterization] mechanical ventilation, and drugs such as vasopressors and paralytic agents) (Table 10, Table S12).[67] There are no validated risk assessment models to stratify VTE risk in critically ill patients.

3.2 Screening for VTE

There are no studies in critically ill patients of the effectiveness of screening compression ultrasonography and subsequent treatment of identified DVT in reducing the rate of subsequent symptomatic thromboembolic complications (Table 11). Indirect evidence provides no support for ultrasonographic screening.[59,60]

3.3 Risk of Bleeding

Although critically ill patients are at increased risk for VTE, they frequently develop bleeding complications in the ICU. Up to 80% of critically ill patients have one or more episodes of bleeding, although most bleeding is minor.[68] The risk of major bleeding in the untreated arm of a prophylaxis trial in critical care patients was 2.7%,[69] but the range in practice is dependent on the case mix. Only few studies have specifically evaluated prognostic factors associated with bleeding complications in critically ill patients (Table 12).[70]

3.4 Randomized Trials of Thromboprophylaxis

Five RCTs have examined pharmacologic prophylaxis in critically ill patients: one of LDUH vs placebo,[71] one of LMWH vs placebo,[69] and three of LDUH vs LMWH (one also included a placebo arm)[11,12,72] (Table S13). LDUH prophylaxis has been studied only in doses of 5,000 units bid.

The trial of LDUH vs placebo reported that LDUH was associated with a reduced risk of asymptomatic DVT (13% vs 29%, respectively; RR, 0.46; 95% CI, 0.22-0.99). Rates of bleeding, PE, and mortality were not reported. The trial of LMWH (nadroparin) vs placebo showed a trend toward reduced asymptomatic DVT with nadroparin (16% vs 28%, respectively; RR, 0.55; 95% CI, 0.30-1.00) but failed to demonstrate or exclude a beneficial or detrimental effect of nadroparin on major bleeding (RR, 2.09; 95% CI, 0.54-8.16; 29 more per 1,000; 95% CI, from 12 fewer to 190 more) or mortality (RR, 1.01; 95% CI, 0.4-2.57). PE was not systematically evaluated.

As both of these trials routinely screened patients for asymptomatic DVT (which are usually treated if detected), and neither study reported PE, a direct estimate of effects on symptomatic VTE is only available from one trial with a very small number of events.[11] For the comparison of LDUH vs placebo, results failed to demonstrate or exclude a beneficial or detrimental effect on symptomatic DVT (RR, 0.89; 95% CI, 0.57-1.41; six fewer per 1,000; 95% CI, from 25 fewer to 24 more) or PE (RR, 0.48; 95% CI, 0.10-2.26; 22 fewer per 1,000 (95% CI, from 38 fewer to 53 more) (Table S14). Similarly, comparing LMWH

Table 10—*[Section 3.1] Summary of Findings: Should Unfractionated Heparin vs Placebo Be Used for DVT Prevention in Critically Ill Adult Patients?*[71]

Outcome	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)[c]	Anticipated Absolute Effects: Baseline Risk	Anticipated Absolute Effects: Risk Difference With UFH (95% CI)
Symptomatic DVT	1,457 (1 RCT) up to 28 d	Moderate due to imprecision[a]	RR, 0.89 (0.57-1.41)	58 per 1,000	6 fewer per 1,000 (25 fewer to 24 more)
Pulmonary embolus	1,457 (1 RCT) up to 28 d	Low due to indirectness[b] and imprecision[a]	RR, 0.48 (0.10-2.26)	42 per 1,000	22 fewer per 1,000 (38 fewer to 53 more)
Death	No data	…	…	…	…
Major bleeding	No data	…	…	…	…

See Table 1 and 4 legends for expansion of abbreviations.

[a]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.

[b]Pulmonary embolus baseline risk was obtained from observational studies whereas the relative risk is from RCT (mix of symptomatic and asymptomatic events)

[c]RR estimated from a mix of symptomatic and asymptomatic events.

Table 11—*[Section 3.2] Summary of Findings: Should LMWH vs Placebo Be Used for DVT Prevention in Critically Ill Adult Patients?*[12,70]

Outcome	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk	Risk difference with LMWH (95% CI)
Symptomatic DVT	1,437 (1 RCT) 5-28 d	Moderate due to serious imprecision[a]	RR, 0.82 (0.51-1.32)	58 per 1,000	6 fewer (from 23 fewer to 22 more)
Pulmonary embolus	1,437 (1 RCT) 5-28 d	Very low due to very serious imprecision[b] and indirectness[c]	RR, 1.01 (0.31-3.31)	42 per 1,000	1 more (from 29 fewer to 97 more)
Death	169 (1 RCT) 5-28 d	Low due to very serious imprecision[a]	RR, 1.01 (0.40-2.57)	94 per 1,000	1 more per 1,000 (from 56 fewer to 148 more)
Major bleeding	221 (1 RCT) 5-28 d	Low due to very serious imprecision[a]	RR, 2.09 (0.54 -8.16)	27 per 1,000	29 more per 1,000 (from 12 fewer to 190 more)

See Table 1 and 4 legends for expansion of abbreviations.

[a]CIs include appreciable harms and benefits.

[b] The RR of the outcome of PE is considered very imprecise due to small number of events (4 of 478 LMWH vs 8 of 959 placebo).

[c]RR estimated from a mix of symptomatic and asymptomatic events.

vs placebo, results failed to demonstrate or exclude a beneficial or detrimental effect of LMWH on symptomatic DVT (RR, 0.82; 95% CI, 0.51-1.32), PE (RR, 1.01; 95% CI, 0.31-3.31), bleeding (RR, 2.09; 95% CI, 0.54-8.16), or mortality (RR, 1.01; 95% CI, 0.4-2.57) (Table S15). Combining data from the above comparisons,[11,69,71] the use of any heparin (LMWH or LDUH) compared with placebo was associated with similar risks of symptomatic DVT, symptomatic PE, major bleeding, and mortality (Table S16; Table 13).

A large randomized, blinded, placebo-controlled trial compared the LMWH dalteparin 5,000 International Units daily vs LDUH 5,000 International Units bid in 3,764 critically ill patients expected to remain in the ICU for ≥ 3 d. The trial failed to demonstrate or exclude difference in the rate of proximal leg asymptomatic DVT (5.1% vs 5.8%, respectively; HR, 0.92; 95% CI, 0.68-1.23).[12] PE was not systematically screened, and PE events were classified by a blinded, independent adjudication committee as definite, probable, possible, or absent. Symptomatic PE occurred in significantly fewer patients receiving dalteparin compared with LDUH (22 of 1,873 [1.2%] vs 38 of 1,873 [2%]; RR, 0.58; 95% CI, 0.34-0.97). The study failed to show differences in major bleeding, rates of HIT, ICU mortality, and hospital mortality in the dalteparin and LDUH groups (major bleeding, 5.5% vs 5.6%; HR, 1.00; 95% CI, 0.75-1.34; HIT, 0.3% vs 0.6%; HR, 0.47; 95% CI, 0.16-1.35; ICU mortality, 15.2% vs 16.2%; HR, 0.97; 95% CI, 0.82-1.15; hospital mortality, 22.1% vs 24.5%; HR, 0.92; 95% CI, 0.80-1.05). Two other trials[11,72] conducted this comparison with variable reporting of symptomatic outcomes (Table 14, Table S17).

The panel considered suggesting LMWH over LDUH; however, the benefit was small enough in magnitude (eight PEs per 1,000 patients prevented by LMWH with lower boundary of the CI of 0.6 PE per 1,000), and the treatment effect was only driven by a difference of 16 events. In addition, this trial performed screening compression ultrasonography on all enrolled patients, which differs from real world practice. If DVTs detected on ultrasonography remained undiagnosed and untreated and progressed to symptomatic PE, the treatment effect would likely be different. The panel decided to not issue this recommendation in the absence of evidence from other future trials and reliable cost-effective data.

There are no randomized trials comparing mechanical methods of prophylaxis (GCS, IPC) with no prophylaxis in critically ill patients. Although combined mechanical and pharmacologic prophylaxis appears to be more effective in reducing symptomatic and asymptomatic VTE events than mechanical methods alone in surgical ICU patients, it is not known whether this is the same in medical ICU patients.[73]

Recommendations

3.2. In critically ill patients, we suggest against routine ultrasound screening for DVT (Grade 2C)**.**

3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C)**.**

3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding (Table 4), we suggest mechanical thromboprophylaxis

Table 12—*Prognostic Factors Associated With Bleeding in ICU Patients*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Comments
Cook et al[70]/2008 (DIRECT)	Multicenter prospective cohort	138 Medical-surgical ICU patients with renal insufficiency	Dalteparin 5,000 International Units SC daily	Daily bedside clinical assessment using ICU bleeding tool	Up to 30 d	Increased INR HR for 0.5-unit difference, 1.68 (95% CI, 1.07-2.66)	Independent variables: baseline characteristics,[a] type of dialysis, INR, aPTT, platelet count, and within preceding 3 d: therapeutic heparin treatment, prophylactic dalteparin, detectable trough anti-Xa level, any dose of aspirin
Arnold et al[68]/2007	Single-center prospective cohort	100 Consecutive medical-surgical ICU patients	None. Daily bleeding assessment done in duplicate by blinded, trained assessors	Fatal bleeding: bleeding causing death. Major bleeding: bleeding causing severe physiologic derangements, occurred at a critical site, or required therapeutic intervention. Minor bleeding: bleeding not meeting criteria for major bleeding	During ICU stay until discharge, death, or 90 d	Most major bleeding events were GI; 90% of patients experienced 480 bleeding events; 94.8% minor and 5.2% major. HRs (95% CI) for predictors of major bleeding: prolonged aPTT 1.2 (1.1-1.3) for every 10 s increase, decrease in platelet count 1.7 (1.2-2.3) for every 50×10^9/L decrease	Risk factors included in the model: admission diagnosis, APACHE II score, platelet count, coagulation parameters, use of prophylactic or therapeutic doses of UFH or LMWH, use of antiplatelet agents, need for dialysis

APACHE = Acute Physiologic and Chronic Health Evaluation; aPTT = activated partial thromboplastin time; INR = international normalized ratio; SC = subcutaneous. See Table 1-4 legends for expansion of abbreviations.

[a]Age, APACHE II score, surgical vs medical admission, pre-ICU renal status.

Table 13—*[Section 3.4.3] Summary of Findings: Should Any Heparin (LDUH, LMWH) vs Placebo Be Used for DVT Prophylaxis in Critically Ill Adult Patients?*[12,70,71]

Outcome	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk	Risk Difference With Any Heparin (95% CI)
Symptomatic DVT	1,935 (1 RCT) 5-28 d	Moderate due to serious imprecision[a]	RR, 0.86 (0.59-1.25)	58 per 1,000	4 fewer per 1,000 (from 12 fewer to 8 more)
Pulmonary embolus	1,935 (1 RCT) 5-28 d	Low due to serious imprecision[a] and indirectness[b]	RR, 0.73 (0.26-2.11)	42 per 1,000	11 fewer per 1,000 (from 31 fewer to 47 more)
Death	169 (1 RCT) 5-28 d	Low due to very serious imprecision[a]	RR, 1.01 (0.40-2.57)	94 per 1,000	1 more per 1,000 (from 56 fewer to 148 more)
Major bleeding	221 (1 RCT) 5-28 d	Low due to very serious imprecision[a]	RR, 2.09 (0.54-8.16)	27 per 1,000	29 more per 1,000 (from 12 fewer to 190 more)

See Table 1 and 4 legends for expansion of abbreviations.
[a]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.
[b]RR estimated from a mix of symptomatic and asymptomatic events.

with GCS (Grade 2C) **or IPC** (Grade 2C) **until the bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis** (Grade 2C)**.**

4.0 Patients With Cancer in the Outpatient Setting

The role of thromboprophylaxis to prevent VTE in patients with cancer undergoing surgery is addressed in the article about prevention of VTE in surgical patients in this supplement.[1]

4.1 Risk of VTE

Patients with cancer have at least a sixfold increased risk of VTE,[16,74] and the development of DVT is associated with a significant reduction in survival in this population.[75-77] VTE risk is higher with certain cancers (malignant brain tumors; adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, and kidney; and hematologic malignancies).[78]

Nonsurgical therapies for cancer, such as chemotherapy and hormonal manipulation, also increase

Table 14—*[Section 3.4.4] Summary of Findings: Should LMWH vs Unfractionated Heparin Be Used for DVT Prevention in Critically Ill Adult Patients?*[12,13,72]

Outcome	Anticipated Absolute Effects		Relative Effect (95% CI)	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)
	Risk with UFH	Risk Difference With LMWH (95% CI)			
Symptomatic DVT	25 per 1,000	3 fewer per 1,000 (from 10 fewer to 6 more)	RR, 0.87 (0.60-1.25)	4,722 (2 RCTs) 7-28 d	Moderate due to imprecision[a]
Symptomatic pulmonary embolism	20 per 1,000	8 fewer per 1,000 (13.2 fewer to 0.6 fewer)	RR, 0.58 (0.34-0.97)	3,746 (1 RCT) 7 d	Moderate due to imprecision[a]
Major bleeding	55 per 1,000	2 fewer per 1,000 (from 14 fewer to 14 more)	RR, 0.97 (0.75-1.26)	3,902 (2 RCTs) 7-47 d	Moderate due to imprecision[a]
Death	159 per 1,000	10 fewer per 1,000 (from 30 fewer to 14 more)	RR, 0.94 (0.81-1.09)	3,902 (2 RCTs) 7-47 d	Moderate due to imprecision[a]
Heparin-induced thrombocytopenia	6 per 1,000	3 fewer per 1,000 (from 5 fewer to 1 more)	RR, 0.42 (0.15-1.18)	3,746 (1 RCT) 7 d	Moderate due to imprecision[a]

See Table 1 and 4 legends for expansion of abbreviations.
[a]We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) or when CIs include appreciable harms and benefits.

the risk of VTE.[16,79-86] The rate of VTE increases by twofold to fivefold among women whose breast cancer has been treated with the selective estrogen receptor modulator tamoxifen.[85,87] This risk was even greater in postmenopausal women when tamoxifen was combined with chemotherapy.[88] The use of aromatase inhibitors anastrozole, letrozole, or exemestane is associated with about one-half the risk of VTE compared with tamoxifen.[89-92] Angiogenesis inhibitors have also been shown to increase thromboembolic complications in patients with cancer.[93] Thalidomide and lenalidomide increase the risk of venous thrombosis, especially when combined with chemotherapy or high-dose dexamethasone.[94-97] A recent meta-analysis reported a high risk of VTE in patients with cancer receiving bevacizumab.[98] Finally, the presence of a CVC in patients with cancer predisposes to upper extremity DVT.[99-101]

4.2 Parenteral Anticoagulants

A recent systematic review evaluated the efficacy and safety of parenteral anticoagulants in outpatients with cancer.[102] The review identified nine eligible RCTs enrolling 2,857 patients with metastatic or locally advanced solid cancers of different tissue types. The intervention consisted of UFH in one study and LMWH in the remaining studies; all studies used prophylactic doses. Type of chemotherapy, duration of treatment, and duration of antithrombotic prophylaxis varied widely among the studies. A number of studies administered heparin for the duration of chemotherapy, whereas other studies administered it for fixed durations of heparin (eg, 6 weeks, 12 months).

Overall, the effect of heparin therapy on mortality was not statistically significant at 12 months (RR, 0.93; 95% CI, 0.85-1.02), but it was statistically significant at 24 months (RR, 0.92; 95% CI, 0.88-0.97) (Table 15, Table S18). Heparin therapy also reduced symptomatic VTE (RR, 0.55; 95% CI, 0.37-0.82). The results failed to confirm or to exclude beneficial or detrimental effects of heparin therapy on major bleeding (RR, 1.30; 95% CI, 0.59-2.88), minor bleeding (RR, 1.05; 95% CI, 0.75-1.46), and quality of life (assessed in only one study[103]). The quality of evidence was high for symptomatic VTE; moderate for mortality, major bleeding, and minor bleeding; and low for quality of life.

In a subgroup analysis of patients with small cell lung cancer (SCLC)[104,105] vs other types of cancer, the test for subgroup effect was statistically significant for mortality at 12 months ($P = .03$) (RR, 0.86; 95% CI, 0.75-0.98 for SCLC vs RR, 0.96; 95% CI, 0.86-1.07

Table 15—*[Section 4.2] Summary of Findings: Should Heparin Compared With No Heparin Be Used for Patients With Cancer Who Have No Other Therapeutic or Prophylactic Indication for Anticoagulation?*[102]

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk, No Heparin	Corresponding Risk, Heparin			
Mortality; follow-up: 12 mo	Medium-risk population		RR, 0.93 (0.85-1.02)	2,531 (8)	Moderate[b-d]
	649 per 1,000	604 per 1,000 (552 to 662)			
Symptomatic VTE; follow-up: 12 mo	Medium-risk population		RR, 0.55 (0.37-0.82)	2,264 (7)	High[b]
	29 per 1,000	16 per 1,000 (11 to 24)			
Major bleeding; follow-up: 12 mo	Medium-risk population		RR, 1.3 (0.59-2.88)	2,843 (9)	Moderate[b,e]
	7 per 1,000	9 per 1,000 (4 to 20)			
Minor bleeding; follow-up: 12 wk	Medium-risk population		RR, 1.05 (0.75-1.46)	2,345 (7)	Moderate[b,e]
	27 per 1,000	28 per 1,000 (20 to 39)			
Health-related quality of life: the Uniscale and the Symptom Distress Scale; better indicated by lower values. Follow-up: 12 mo	Not estimable	Not estimable	Not estimable[f]	0 (1)	Low[g]

See Table 4 legend for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Vast majority of studies had allocation concealment and used blinded outcome and adjudication. We did not downgrade, although there was some concern about lack of blinding in some studies; the overall risk of bias was believed to be very low.

[c]There is moderate heterogeneity among studies included in the analysis of death at 12 mo ($I^2 = 41\%$). The subgroup analysis for mortality at 12 mo was statistically significant and suggested survival benefit in patients with small cell lung cancer but not in patients with advanced cancer. Overall we decided to downgrade by one level when considering these issues along with imprecision.

[d]CI interval includes effects suggesting benefit as well as no benefit.

[e]CI includes possibility of both harms and benefits.

[f]The scores for the two scales were similar for the two study groups, both at baseline and at follow-up.

[g]High risk of bias and only 138 patients enrolled.

for other types of cancer) but not statistically significant at 24 months ($P = .88$). In a subgroup analysis of patients with advanced cancer vs patients with non-advanced cancer, the review found no significant difference between the effects of heparin in the two subgroups ($P = .51$).

In summary, there is moderate-quality evidence of a reduction in mortality and high-quality evidence of a reduction in VTE with larger absolute effects than any plausible increase in risk of major bleeding. There is a possible but not convincing increased mortality benefit in the subgroup of patients with SCLC.

4.3 Oral Anticoagulants

A recent systematic review evaluated the efficacy and safety of oral anticoagulants in patients with cancer and no therapeutic or prophylactic indication for anticoagulation.[106] The review identified five eligible RCTs that enrolled 1,656 patients. The intervention consisted of warfarin in all five studies; started within a month before, or at the time of, initiating chemotherapy; and continued until the end of chemotherapy or up to a few weeks later.

Warfarin had little or no effect on reducing mortality at 6 months (RR, 0.96; 95% CI, 0.80-1.16), at 1 year (RR, 0.94; 95% CI, 0.8-1.03), at 2 years (RR, 0.97; 95% CI, 0.87-1.08), or at 5 years (RR, 0.91; 95% CI, 0.83-1.01). One study assessed the effect of warfarin on VTE and showed an RR reduction of 85% (RR, 0.15; 95% CI, 0.02-1.2; 25 fewer per 1,000 [from 28 fewer to six more]). Warfarin increased both major bleeding (RR, 4.24; 95% CI, 1.85-9.68; 23 more per 1,000 [from six more to 61 more]) and minor bleeding (RR, 3.34; 95% CI, 1.66-6.74). The quality of evidence was moderate for all outcomes (Table 16, Table S19). In summary, the absolute risk increase of bleeding with warfarin outweighs the absolute risk reduction of VTE.

4.4 Patients With Cancer With Indwelling CVCs

CVCs may result in arm swelling and discomfort, PE, predisposition to catheter-related sepsis, and the need to replace the catheter.[107,108] Peripherally inserted CVCs are associated with a greater risk of thrombosis than subclavian vein or internal jugular vein access.[109,110] If the CVC tip is placed in the upper superior vena cava or more peripherally, the DVT risk is higher than when placed at or just above the right atrium.[111] Other potential risk factors include left-sided CVC insertion, chest radiotherapy, more than one insertion attempt, and previous CVC insertion.[112,113]

A systematic review identified 12 eligible RCTs that enrolled 3,611 patients with cancer and an indwelling CVC[114] and compared prophylactic-dose heparin (LDUH or LMWH) or low-dose VKAs to each other or to no anticoagulation. Most studies administered treatments for a specified fixed period or until CVC removal or thrombosis diagnosis.

Prophylactic-dose heparin was associated with a trend toward reduction in symptomatic DVT (RR, 0.54; 95% CI, 0.28-1.05) (Table 17, Table S20). The results failed to confirm or to exclude beneficial or detrimental effects of prophylactic-dose heparin on

Table 16—*[Section 4.3] Summary of Findings: Should Oral Anticoagulation Be Used in Patients With Cancer With No Therapeutic or Prophylactic Indication for Anticoagulation?*[102]

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk, Control	Corresponding Risk, Oral Anticoagulation			
Death; follow-up: median 1 y	457 per 1,000	430 per 1,000 (398- 471)	RR, 0.94 (0.87-1.03)	1,604 (5)	Moderate[b]
VTE; follow-up: 1 y	43 per 1,000	6 per 1,000 (1-52)	RR, 0.15 (0.02-1.2)	315 (1)	Moderate[c]
Major bleeding; follow-up: median 1 y	22 per 1,000	93 per 1,000 (41-213)	RR, 4.24 (1.85-9.68)	1,282 (4)	Moderate[d]
Minor bleeding; follow-up: 1 y	79 per 1,000	264 per 1,000 (131-532)	RR, 3.34 (1.66-6.74)	851 (3)	Moderate[d]
Health-related quality of life: not reported	Not estimable	Not estimable	Not estimable	…	Not estimable

See Table 1 and 4 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]We downgraded because of lack of blinding of patients and providers in four out of five studies, it was unclear whether allocation was concealed in two studies, and only one study clearly used ITT analysis.

[c]We downgraded because the precision of the estimate does not exclude a patient-important benefit (the lower limit of RR still suggests a benefit that might be relevant given the high baseline risk).

[d]We downgraded because lack of blinding of patients and providers in three out of four studies, it was unclear whether allocation was concealed in two studies, and only one study clearly used ITT analysis.

death (RR, 0.85; 95% CI, 0.53-1.37), major bleeding (RR, 0.68; 95% CI, 0.10-4.78), thrombocytopenia (RR, 0.85; 95% CI, 0.49-1.46), and infection (RR, 0.91; 95% CI, 0.49-1.68). No data were available for HIT, heparin-induced thrombocytopenia and thrombosis, PE, or catheter failure. The quality of evidence was moderate for all outcomes.

Results failed to confirm or to exclude beneficial or detrimental effects of low-dose VKAs on death (RR, 0.97; 95% CI, 0.82-1.15), symptomatic DVT (RR, 0.63; 95% CI, 0.35-1.11), or major bleeding (RR, 6.93; 95% CI, 0.86-56.08) (Table 18, Table S21). However, low-dose VKAs were associated with a statistically significant reduction in asymptomatic DVT (RR, 0.42; 95% CI, 0.28-0.61).

Studies comparing heparin to VKA found no effects on any of the outcomes of interest. The quality of evidence was low for all these outcomes (Table 19, Table S22).

In summary, prophylactic-dose heparin in patients with cancer and CVCs is potentially associated with more benefits than harms. It is uncertain whether the potential benefits of low-dose VKAs outweigh the associated potential increase in bleeding.

Despite evidence of benefit of prophylactic-dose heparin in some outpatients with cancer and some patients with cancer with CVCs, the substantial clinical heterogeneity of the patients studied (different cancer types, different cancer treatments, and different durations of prophylaxis) raises questions about which groups of outpatients with cancer will benefit. More evidence will be available over the next few years on the effectiveness, cost-effectiveness, and specific patient groups most likely to benefit from prophylaxis. Considering the selection criteria of the studies, patients with solid cancer, high risk for VTE, and low risk of bleeding are more likely to benefit than be harmed from heparin prophylaxis.

Recommendations

4.2.1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and recommend against the prophylactic use of VKAs** (Grade 1B)**.**

Remarks: Additional risk factors for venous thrombosis in outpatients with cancer include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B)**.**

Remarks: Additional risk factors for venous thrombosis in outpatients with cancer include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.

4.4. In outpatients with cancer and indwelling CVCs, we suggest against routine prophylaxis with LMWH or LDUH (Grade 2B) **and suggest against the prophylactic use of VKAs** (Grade 2C)**.**

5.0 Chronically Immobilized Outpatients

5.1 Risk of VTE

The recognition that bedbound hospitalized patients are at increased risk for VTE has led many clinicians

Table 17—*[Section 4.4] Summary of Findings: Should Heparin Compared With No Heparin Be Used for Thrombosis Prophylaxis in Patients With Cancer With Central Venous Catheters?*[114]

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk, No Heparin	Corresponding Risk, Heparin			
Death	65 per 1,000	55 per 1,000 (34-89)	RR, 0.85 (0.53-1.37)	1,192 (5)	Moderate[b-d]
Symptomatic DVT	49 per 1,000	26 per 1,000 (14-51)	RR, 0.54 (0.28-1.05)	1,173 (6)	Moderate[b-d]
Major bleeding	5 per 1,000	3 per 1,000 (1-24)	RR, 0.68 (0.1-4.78)	891 (4)	Moderate[b-d]
Infection	71 per 1,000	65 per 1,000 (35-119)	RR, 0.91 (0.49-1.68)	626 (3)	Moderate[b,c]
Thrombocytopenia	66 per 1,000	56 per 1,000 (32-96)	RR, 0.85 (0.49-1.46)	836 (3)	Moderate[b-d]
Quality of life: not reported	Not estimable	Not estimable	Not estimable	…	Not estimable

See Table 4 for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Allocation clearly concealed in three of the six studies. Four studies blinded patients and providers and all studies blinded outcome adjudicators. Three studies had no problem with incomplete data. None of the studies was suspected of selective reporting. Two studies clearly used ITT.

[c]Relatively small number of events.

[d]CI includes both values suggesting no effect and values suggesting either benefit or harm.

Table 18—*[Section 4.5] Summary of Findings: Should VKA Compared With No VKA Be Used for Thrombosis Prophylaxis in Patients With Cancer With Central Venous Catheters?*[114]

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk, no VKA	Corresponding Risk, VKA			
Death	312 per 1,000	303 per 1,000 (256-359)	RR, 0.97 (0.82-1.15)	1,093 (2)	Moderate due to imprecision[b,c]
Symptomatic DVT	90 per 1,000	57 per 1,000 (31-100)	RR, 0.63 (0.35-1.11)	1,235 (4)	Moderate due to imprecision[b,c]
Major bleeding	2 per 1,000	14 per 1,000 (2-112)	RR, 6.93 (0.86-56.08)	1,093 (2)	Moderate due to imprecision[b,c]; high-quality evidence in other populations

See Table 1 and 4 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]We did not rate down for methodologic limitations. Allocation clearly concealed in three of the four studies. None of studies blinded patients, providers, or data collectors, and three studies blinded outcome adjudicators. Three studies had no problem with incomplete data. The presence of selective reporting was unclear in one study. Two studies clearly used ITT.

[c]Relatively small number of events. CI includes both values suggesting no effect and values suggesting either benefit or harm.

to consider whether chronically immobilized outpatients are at similar increased risk, and whether they may also benefit from VTE prophylaxis. The chronically immobile population is large and includes patients who are homebound, as well as residents of nursing homes and postacute care facilities. Despite their similarities to medical inpatients, there have been few studies and no placebo-controlled trials investigating VTE prophylaxis for chronically immobilized outpatients.

Although the population at risk is clearly large, the scope of the problem and incidence of symptomatic VTE is uncertain. One study of outpatients examined the incidence of symptomatic VTE in 16,532 outpatients > 40 years of age (median age, 71 years) who were not immobile at baseline and had an acute medical condition reducing mobility for at least 48 h.[115] Anticoagulant prophylaxis was administered to 35% of patients. The study found a 1.2% incidence of symptomatic VTE in the 3 weeks after the onset of the acute condition. This incidence is similar to studies examining patients hospitalized with acute medical conditions, but the pattern of immobility (acute rather than chronic) does not allow extrapolation to homebound patients.

Several observational studies have examined the incidence of VTE in nursing home patients, including two large studies using the Minimum Data Set, a mandatory questionnaire completed for all Medicare-licensed long-term facilities in the United States.[116,117] Liperoti and colleagues retrospectively assessed 132,018 nursing home patients across five states

Table 19—*[Section 4.6] Summary of Findings: Should LMWH Compared With VKA Be Used for Thrombosis Prophylaxis in Patients With Cancer With Central Venous Catheters?*[114]

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk, VKA	Corresponding Risk, LMWH			
Death	110 per 1,000	140 per 1,000 (61-326)	RR, 1.27 (0.55-2.96)	343 (2)	Low[b-d]
Symptomatic DVT	22 per 1,000	28 per 1,000 (6-143)	RR, 1.28 (0.25-6.5)	280 (2)	Low[b-d]
Major bleeding	0 per 1,000	0 per 1,000 (0-0)	RR, 3.1 (0.13-73.14)	343 (2)	Low[b-d]
Thrombocytopenia	0 per 1,000	0 per 1,000 (0-0)	RR, 5.17 (0.26-103.21)	59 (1)	Low[b-d]
Quality of life: not reported	Not estimable	Not estimable	Not estimable	…	Not estimable

See Table 1 and 4 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Allocation clearly concealed in one of the two studies. None of the studies blinded patients, providers, or data collectors, but both studies blinded outcome adjudicators. One study did not address incomplete data reporting. None of the studies was suspected of selective reporting. One study clearly used ITT.

[c]Relatively small number of events.

[d]CI includes both values suggesting no effect and values suggesting either benefit or harm.

and found a symptomatic VTE incidence of 0.91 per 100 person-years. Similarly, a retrospective study of 18,661 nursing home patients in Kansas found a VTE incidence of 1.30 per 100 person-years.[116] These studies suggest that the best estimate of the annual incidence of symptomatic VTE in nursing home patients is approximately 1%. The use of anticoagulant prophylaxis has not been examined adequately in this population to draw conclusions on whether the benefits outweigh the risks and costs.

The incidence of VTE in postacute care facilities was examined in a prospective cohort study of 3,039 patients admitted for rehabilitation after acute medical illness or surgery.[118] Reasons for admission to the facility included medical illness (54.7%), stroke (21.1%), and surgery (31.7%). Most patients (75.1%) received anticoagulant thromboprophylaxis, which was primarily LMWH. The incidence of symptomatic VTE was 2.4% during the stay at the facility (median duration 26 days). Risk factors for VTE were cancer and prior VTE.

Two cross-sectional studies examined the prevalence of asymptomatic DVT in elderly patients in postacute care facilities in France and detected asymptomatic DVT in 14.0% and 15.8% of patients, respectively.[119,120] A subsequent analysis that combined data from these two studies noted that although proximal DVT was not significantly reduced among patients who received LMWH prophylaxis (5.7% vs 4.0%; $P = .16$), this difference became statistically significant with the use of propensity analysis to control for potentially confounding variables (OR, 0.56; $P = .03$).[121] These studies suggest that the incidence of asymptomatic DVT in elderly patients in postacute care facilities is similar to that of hospitalized patients. However, their observational designs and lack of patient-important end points does not allow for any conclusions to be drawn on whether thromboprophylaxis is of benefit in this population (Table S23).

The available data suggest that nursing home patients have an incidence of symptomatic VTE of 1% annually and postacute care patients have an incidence of 1.0% to 2.4% during their stay at the facility. These data offer some indirect support for prophylaxis of immobile patients in postacute or subacute care facilities, as their incidence of VTE may be similar to that of acutely ill hospitalized patients. Randomized trials are needed to determine if the benefits of anticoagulant thromboprophylaxis outweigh the risks in this population.

Recommendation

5.1. In chronically immobilized persons residing at home or at a nursing home, we suggest against the routine use of thromboprophylaxis (Grade 2C)**.**

6.0 Long-Distance Travel

6.1 Risk of VTE

Prolonged air travel results in a very small absolute incidence of VTE. A systematic review and meta-analysis of 14 studies (11 case-control, two cohort, and one case-crossover) of risk for VTE in travelers demonstrated a pooled RR of 2.8 (95% CI, 2.2-3.7). A dose-response relationship was identified, with an 18% higher risk of VTE for each 2-h increase in travel duration.[122,123] However, the overall absolute incidence of a symptomatic VTE in the month following a flight > 4 h is 1 in 4,600 flights,[124] with a reported incidence of asymptomatic VTE on arrival from a trip ranging from 0% to 1.5%.[123] The incidence varies by the type and duration of travel and by individual risk factors.[125-127] Thrombosis risk also appears to be increased for travel by car, bus, or train.[128-130]

The association between air travel and VTE is strongest for flights > 8 to 10 h[125-128,131-133] and is increased in the presence of VTE risk factors such as recent surgery.[123] For those on flights > 4 h, immobility during the flight and window seating (especially for obese persons) also increase the risk of VTE.[134] Especially tall or short passengers may have an increased risk.[130] There is no definitive evidence that dehydration, travel in economy class, and drinking alcoholic beverages on the flight are related to VTE risk.

Most individuals with travel-associated VTE have one or more known risk factors for thrombosis, including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or a thrombophilic disorder.[129,130,132,135-140] Among healthy volunteers, coagulation activation observed after an 8-h flight was greater in carriers of factor V Leiden and in women taking oral contraceptives.[141] Case-control studies have reported an increased risk of VTE in travelers who have thrombophilia and use oral contraceptives.[130,136]

We identified a Cochrane review[142] of nine RCTs of thromboprophylaxis in long-distance air travelers (Tables S24, S25). All but one of these trials was conducted by a single group of investigators.[140,143-150] Trials enrolled a mix of low- and increased-risk subjects based on risk factors for VTE, and most studies included persons taking flights of > 7 h. Asymptomatic DVT detected by screening ultrasound examination was the primary end point. All of the trials have methodologic limitations that compromise their interpretation. Further, the UK General Medical Council's Fitness to Practice Panel judged that these papers included coauthors who had not approved the papers and erased the principal investigator from the register of the General Medical Council.[151] Regardless, as there

was no evidence presented suggesting falsification of data, we include discussion of these trials in this article.

A meta-analysis of the above trials found that among nine randomized trials,[142] the use of various brands of below-knee GCS (providing 15-30 mm Hg compression at the ankle) reduced the rate of asymptomatic DVT detected by screening from 3.6% (47 of 1,323 control subjects) to 0.2% (three of 1,314 stocking users) (RR, 0.10; 95% CI, 0.04-0.25); absolute estimated effects in a low-risk population were 4.5 fewer symptomatic DVT per 10,000 (95% CI, from four fewer to five fewer) and 24 fewer PE per 1,000,000 (95% CI, from 20 fewer to 26 fewer), and in a high-risk population, 16.2 fewer symptomatic DVT per 10,000 (95% CI, from 14 fewer to 17.5 fewer) and 87 fewer PE per 1,000,000 (95% CI, from 76 fewer to 94 fewer) (Table 20, Table S26). Among eight trials that reported superficial thrombophlebitis as an end point, results failed to show or exclude a beneficial or detrimental effect of stockings (RR, 0.45; 95% CI, 0.18-1.13). Stockings reduced postflight leg edema in six trials in which this outcome was assessed; however, lack of blinding and use of unvalidated measures of edema reduce confidence in this result.

In a small study of high-dose enoxaparin (1 mg/kg), administered once 2 to 4 h before travel lasting 7 to 8 h, vs aspirin, one dose daily for 3 days starting 12 h before the beginning of the flight, vs control, there were zero of 82, three of 84, and four of 83 asymptomatic DVT in the three groups, respectively, but no symptomatic DVT or PE events in any group, although follow-up ended after the subjects left the airport.[149]

In summary, symptomatic VTE is rare in passengers returning from long flights. Travelers at increased risk of VTE, defined as persons with previous VTE, thrombophilic disorders, severe obesity, recently active cancer, or recent major surgery, who are traveling on flights > 6 h, may want to consider reducing their risk of VTE by frequent ambulation or sitting in an aisle seat if feasible and avoiding dehydration, although these measures have not been assessed in clinical trials. Light compression stockings appear to have a protective effect in reducing asymptomatic DVT in travelers, are inexpensive, and are unlikely to cause harm. Until further, methodologically appropriate studies are available, decisions regarding pharmacologic thromboprophylaxis for travelers who are considered to be at particularly high risk for VTE must be made on an individual basis, considering that adverse effects may outweigh any benefit.

Recommendations

6.1.1. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest frequent ambulation, calf muscle exercise or sitting in an aisle seat if feasible (Grade 2C)**.**

6.1.2. For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), we suggest use of properly fitted, below-knee GCS providing 15 to 30 mm Hg of pressure at the ankle stockings during travel (Grade 2C)**. For all other long-distance travelers, we suggest against the use of GCS** (Grade 2C)**.**

6.1.3. For long-distance travelers, we suggest against the use of aspirin or anticoagulants to prevent VTE (Grade 2C)**.**

7.0 Thromboprophylaxis to Prevent VTE in Asymptomatic Persons With Thrombophilia

7.1 Risk of VTE

Thrombophilia refers to inherited or acquired conditions, measurable in the blood, that are associated with an increased risk of developing venous thrombosis. Inherited conditions include factor V Leiden (R506Q) mutation (average population prevalence, 5%; RR of a first venous thrombosis, compared with the general population, 5-7), prothrombin gene (G20210A) mutation (2%; RR, 2-3), antithrombin deficiency (0.04%; RR, 15-20), protein C deficiency (0.3%; RR, 15-20), and protein S deficiency (0.3%; RR, 15-20). Acquired thrombophilic conditions include antiphospholipid antibodies (APLA) (1%-5.6%; RR, 3-10),[9,152] which may be associated with both venous and arterial thrombosis.

Thrombophilia is most often tested for and detected in patients who have been diagnosed with VTE. However, in some situations, asymptomatic persons (ie, without a previous history of VTE) may undergo testing for thrombophilia for reasons potentially related (eg, family member had VTE) or unrelated (eg, as part of a workup for autoimmune disease) to risk of VTE. The absolute annual incidence of VTE in asymptomatic persons with thrombophilia who are relatives of probands with VTE is low, ranging from 0.1% per year for carriers of factor V Leiden, to 1.7% per year for those with antithrombin deficiency or mixed thrombophilic defects.[153,154]

A pertinent clinical question is whether long-term antithrombotic therapy should be offered to such

Table 20—*[Section 6.1] Summary of Findings: Should Compression Stockings Compared With No Compression Stockings Be Used by People Taking Long Flights?*[142]

Outcome	No. of Patients (Studies)	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk Without Stocking	Risk Difference With Stocking (95% CI)
Symptomatic DVT	2,637 (9)	Moderate due to imprecision[a]	Not estimable	0 per 1,000	−1.5% to 1.5%
Pulmonary embolism	2,637 (9)	Not estimable	Not estimable	0 per 1,000	−1.5% to 1.5%
Symptomatic DVT (inferred from surrogate, symptomless DVT)	2,637 (9)	Moderate due to indirectness[b]	RR, 0.10 (0.04-0.25)	Low-risk population[c]	
				5 per 10,000	0.5 per 10,000 (0 to 1.25)
				High-risk population[c]	
				18 per 10,000	1.8 per 10,000 (1 fewer to 8 fewer)
Symptomatic pulmonary embolism (inferred from surrogate, symptomless DVT)	2,637 (9)	Moderate due to indirectness[b]	RR, 0.10 (0.04-0.25)	Low-risk population[c]	
				27 per million	3 per million (1 fewer to 7 fewer)
				High-risk population[c]	
				97 per million	10 per million (4 fewer to 95 fewer)
Superficial vein thrombosis	1,804 (8)	Moderate due to imprecision	RR, 0.45 (0.18-1.13)	13 per 1,000	6 per 1,000 (2 fewer to 15 more)
Edema postflight values measured on a scale from 0, no edema, to 10, maximum edema.	1,246 (6)	Low[b] due to risk of bias (unblinded, unvalidated measure)	Not estimable	The mean edema score ranged across control groups from 6.4 to 8.9	The mean edema score in the intervention groups was on average 4.72 lower (95% CI, 4.91-4.52).
Death	2,637 (9)	Not estimable[d]	Not estimable	Estimates not available, but risk extremely low	
Adverse effects	1,182 (4)	Not estimable[d]	Not estimable	Not estimable	Not estimable

All the stockings in the nine trials included in this review were below-knee compression stockings. In four trials the compression strength was 20-30 mm Hg at the ankle. It was 10-20 mm Hg in the other four trials. Stockings come in different sizes. If a stocking is too tight around the knee it can prevent essential venous return, causing the blood to pool around the knee. Compression stockings should be fitted properly. A stocking that is too tight could cut into the skin on a long flight and potentially cause ulceration and increased risk of DVT. Some stockings can be slightly thicker than normal leg covering and can be potentially restrictive with tight footwear. It is a good idea to wear stockings around the house prior to travel to ensure a good, comfortable fitting. Stockings were put on 2 to 3 h before the flight in most of the trials. The availability and cost of stockings can vary. See Table 4 legend for expansion of abbreviations.

[a]The imprecision refers to absolute measures, not the relative. For the relative, it is not possible to make an estimate. This is also true for pulmonary embolism.

[b]There are two reasons for indirectness: estimates of relative risk reduction come from the surrogate, and there is uncertainty regarding the baseline risk.

[c]Estimates for control event rates for venous thrombosis and for pulmonary embolism come from Philbrick et al.[131] Definition of high risk includes previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous 2 years, or large varicose veins.

[d]None of the other trials reported adverse effects, apart from four cases of superficial vein thrombosis in varicose veins in the knee region that were compressed by the upper edge of the stocking in one trial.[131]

patients to prevent VTE (consideration of antithrombotic therapy to prevent VTE in pregnant women with thrombophilia is addressed in Bates et al[155]). Observational studies have addressed the effects of ASA in asymptomatic persons with APLA, or ASA and hydroxychloroquine in persons with systemic lupus erythematosus and APLA[156-158]; some suggest that these drugs may be effective.

Only one published RCT has addressed this issue. The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study was a randomized, blinded, placebo-controlled clinical trial in asymptomatic patients with APLA comparing the efficacy of aspirin 81 mg daily vs placebo to prevent arterial or venous thrombosis.[159] A total of 98 asymptomatic individuals with persistently positive APLA (> 95% female; 60% had systemic lupus erythematosus) who were not receiving warfarin were randomized. The study failed to demonstrate or exclude a beneficial or detrimental effect of ASA (HR, 1.04; 95% CI, 0.69-1.56). In asymptomatic persons with other types of thrombophilia (factor V Leiden, prothrombin G20210A mutation), a subgroup analysis of the Women's Health Study also failed to demonstrate or exclude an effect of ASA on VTE (HR, 0.83; 95% CI, 0.50-1.39)[160] (Table 21, Tables S27-S30). There are no published studies of the

Table 21—*[Section 7.1] Summary of Findings: Should Aspirin vs No Treatment Be Used for Prevention of VTE in Persons With Asymptomatic Thrombophilia?*[157-160]

Outcome	No. of Patients (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk	Risk Difference With Aspirin (95% CI)
Symptomatic nonfatal DVT and PE	98 (2 RCTs) 2.3-10.1 y	Low due to very serious imprecision[a]	RR, 2.08 (0.20-22.23)	20 per 1,000	22 more per 1,000 (from 16 fewer to 425 more)
Mortality	98 (1 RCT) 2.3 y	Very low due to very serious imprecision[a] and methodologic limitations[b]	RR, 1.04 (0.07-16.19)	21 per 1,000	1 more per 1,000 (from 19 fewer to 316 more)
Major bleeding	207 (3 Observational studies) 2.3-8 y	Very low due to very serious imprecision[a]	Not estimable, no events in either arm	0 per 1,000	Not estimable

See Table 1 and 4 legends for expansion of abbreviations.

[a]Very small number of events.

[b]Erkan et al[159] terminated early as event rates were lower than expected and larger sample size was infeasible.

effectiveness of thromboprophylaxis in asymptomatic persons with thrombophilia types other than APLA, factor V Leiden, or prothrombin mutation, and no studies of anticoagulants such as LMWH, UFH, or VKA, or of mechanical thromboprophylaxis such as GCS to prevent VTE in asymptomatic persons with thrombophilia.

Recommendation

7.1. In persons with asymptomatic thrombophilia (ie, without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)**.**

8.0 Statins to Prevent VTE in Asymptomatic Persons

8.1 Risk of VTE

Statins reduce coagulation potential by decreasing tissue factor expression and decreasing thrombin generation,[161] leading to consideration of statin use to prevent VTE. Statin use has been related to risk of VTE in three prospective cohort studies, six case-control studies, and one clinical trial (Tables S31, S32). Considering DVT and PE together, the pooled risk estimate with statin use vs nonuse from several case-control studies[162-166] was 0.61 (95% CI, 0.48-0.81). Two observational studies based on administrative data[166,167] reported no significant difference in the adjusted OR of VTE comparing statin users and nonusers. In contrast, another observational study[168] reported a lower risk of DVT with statin use, with an RR of 0.78 (95% CI, 0.69-0.87). The Heart and Estrogen/Progestin Replacement (HERS) clinical trial[169] of women with coronary artery disease also reported a lower risk of VTE with statin use (not randomized) in women (HR, 0.45; 95% CI, 0.23-0.88).

A single RCT comparing statin to placebo reported a lower risk of VTE with the statin.[170] The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Using Rosuvastatin (JUPITER) was designed to assess the efficacy of rosuvastatin in preventing arterial vascular events in those not otherwise eligible for statins based on existing guidelines. Thus, it included a large sample of healthy people with low-density lipoprotein cholesterol $<$ 130 mg/dL and C-reactive protein $>$ 2 mg/L, without diabetes

Table 22—*[Section 8.1] Summary of Findings: Should Statins Be Used to Prevent VTE?*[170]

Outcome	No. of Patients (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Baseline Risk	Risk Difference With Statins (95% CI)
Symptomatic DVT	17,802 (1 RCT) 1.9 y	High	HR, 0.45 (0.25-0.79)	4 per 1,000	2 fewer per 1,000 (from 1 fewer to 3 fewer)
Nonfatal PE	17,802 (1 RCT) 1.9 y	High	HR, 0.77 (0.41-1.45)	2 per 1,000	0 fewer per 1,000 (from 1 fewer to 1 more)

See Table 1 and 2 legends for expansion of abbreviations.

and other conditions. Considering symptomatic VTE, a secondary end point of the trial, assignment to the statin was associated with a 55% lower DVT risk and 23% lower PE risk. There was no increased risk of bleeding. The absolute rates of VTE were 2 per 1,000 in statin users compared with 4 per 1,000 in nonusers. The number needed to treat to prevent one DVT was 500 (Table 22, Table S33).

The panel considered that it was premature to issue a recommendation concerning the use of statins to prevent VTE in light of the paucity of data and the availability of more established effective treatments. In addition, the patients included in this trial were not at increased risk of thrombosis and are not the patients for whom thromboprophylaxis would be recommended.

This area is in need of further research. Trials that enroll patients at high risk of VTE (eg, those with previous VTE) who require thromboprophylaxis are needed. Such trials should have a comparative effectiveness design to better inform guideline developers; to that extent, these trials should have an active treatment of comparison, focus on symptomatic events that matter the most to patients, and report cost effectiveness analyses.

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Dr Dunn: contributed as a panelist.
Dr Cushman: contributed as a panelist.
Dr Dentali: contributed as a panelist.
Dr Akl: contributed as a panelist.
Dr Cook: contributed as a panelist.
Dr Balekian: contributed as a resource consultant.
Dr Klein: contributed as a frontline clinician.
Dr Le: contributed as a frontline clinician.
Dr Schulman: contributed as a panelist.
Financial/nonfinancial disclosures: The authors of this guideline provided detailed conflict of interest information related to each individual recommendation made in this article. A grid of these disclosures is available online at http://chestjournal.chestpubs.org/content/141/2_suppl/e195S/suppl/DC1. In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Kahn has received peer-reviewed and investigator-initiated industry research funding for projects related to venous thrombosis and postthrombotic syndrome prevention and treatment. She has received honoraria for industry-sponsored talks pertaining to venous thrombosis. Dr Balekian received industry research support and served as a consultant in areas relating to venous thrombosis. Dr Cook has received donated study drug (dalteparin) from Pfizer for a Canadian government-funded trial of thromboprophylaxis in the ICU. Dr Cushman is the mentor on a mentored research grant from the Hemophilia and Thrombosis Research Society that is studying risk factors for venous thrombosis among medical inpatients, 2009-2011. No specific dollar amount goes toward her salary. Dr Akl is a prominent contributor to the GRADE Working Group. Dr Murad is a member of the GRADE Working Group. Drs Lim, Dunn, Dentali, Klein, Le, and Schulman have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.
Endorsements: This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.
Additional information: The supplemental Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e195S/suppl/DC1.

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CHEST Online Data Supplement

Prevention of VTE in Nonsurgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—*Eligibility Criteria for RCTs of Thromboprophylaxis vs Placebo/Control in Hospitalized Medical Patients*

Study/Year	Inclusion Criteria	Exclusion Criteria
Gallus et al[1]/1973	Age N/S (Study participants were 43-85 y; mean age not available)	History of DVT or PE within previous y
	Hospitalized	Bleeding tendency
	Heart failure	
Belch et al[2]/1981	Age 40-80 y (mean age not available)	Bed rest for > 2 d before admission
	Hospitalized	DVT or PE on admission
	Heart failure, chest infection, or both	High risk for bleeding
		Iodine allergy/sensitivity
Dahan et al[3]/1986	Age > 65 y (mean ± SD age: treatment group, 79.9 ± 6.8 y; placebo group, 80.1 ± 6.9 y)	Predictable short-term hospitalization (< 7 d)
	Hospitalized	Active bleeding
		Coagulation disorder
		Thyroid disease
		Ongoing anticoagulant or antiplatelet therapy
		Iodine allergy
	Acute medical illness: CHF (NYHA III-IV), acute or respiratory infectious disease	"Autopsy not available if necessary"
Ibarra-Perez et al[4]/1988	Age > 40 y (mean age not available)	PE
	Predicted immobilization > 3 d	Medical history of DVT or PE
		Hemorrhage
		CVA
		Vasculitis
		Pericarditis
		Coagulation disorders
		Recent postoperative status
		Use of anticoagulants
	Hospitalized	Allergy to iodine
	Pulmonary disease	Patient or physician's refusal to cooperate

(Continued)

Table S1—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Gardlund[5]/1996	Age > 55 y (mean age 75 y)	Ability to be mobile
		Readmission within 60 d of randomization
		Active bleeding
		Persistent hemorrhage or increased risk of bleeding complications (eg, inherited bleeding disorders, platelet count $< 70 \times 10^9$/L, or history of intraocular bleeding)
		Severe renal failure (requiring dialysis)
		Liver failure
		HIV infection
		Terminal disease in which active treatment was withheld
		Preexistent anticoagulant therapy (heparins or coumarin)
	Hospitalized	Heparin prophylaxis judged to be indicated by the responsible doctor
	Infectious disease (pneumonia, skin and soft-tissue infections, fever/sepsis, UTI, gastroenteritis, upper respiratory tract infection, and so forth)	Assessment of contraindications not possible (eg, patient comatose and no next of kin was available)
Bergmann and Caulin[6]/1996	Age N/S (mean age 76 y)	Not stated
	Immobile (confined to bed)	
	Hospitalized < 24 h before study inclusion	
	Acute medical illness (acute cardiac disease, 25%; acute pulmonary disease, 22%; cancer, 14%; nonpulmonary sepsis, 23%)	

(Continued)

Table S1—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Samama et al,[7] MEDENOX Study/1999	Age > 40 y (mean ± SD age: 20 mg enoxaparin group, 72.9 ± 10.1 y; 40 mg enoxaparin group, 73.1 ± 10.8 y; placebo group, 74.1 ± 10.6 y)	Known thrombophilia
	Immobilization < 3 d at time of enrollment	Serum creatinine concentration > 1.7 mg/dL (150 μmol/L)
	Projected hospital stay > 6 d	Uncontrolled arterial hypertension (systolic BP > 200 mm Hg, diastolic BP > 120 mm Hg, or both)
		Active peptic ulcer, bacterial endocarditis, or other conditions that could increase the risk of hemorrhage
		Platelet count < 100,000/μL, prolonged aPTT, prothrombin ratio of < 50%, or INR > 1.2
		HIV
		Stroke/surgery within previous 3 mo
		Intubation
		Anticoagulant therapy required/received any type of anticoagulant therapy for > 48 h
		Contraindications to iodinated contrast media
		Hypersensitivity to heparin or heparin-induced thrombocytopenia
	CHF (NYHA III-IV), acute or chronic respiratory disease (if acute respiratory failure does not require ventilator support); or one of the following acute infectious or rheumatologic disease, if associated with at least one additional risk factor[a] for VTE: acute infection without septic shock; acute rheumatic disorders (including acute lumbar pain or sciatica or vertebral compression caused by osteoporosis or a tumor), acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease	Pregnant/breastfeeding women
		Women of childbearing age not using contraception

(Continued)

Table S1—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Fraisse et al[8]/2000	Age 40-80 y (mean ± SD age: treatment group, 69.4 ± 7.7 y; placebo group, 66.8 ± 8.2 y)	Patient on ventilator < 48 h
	Hospitalized (medical ICU)	History of a confirmed DVT within the previous 6 mo or presence of signs of a DVT on the Doppler ultrasonography at inclusion
	Admitted with acute, respiratory-decompensated COPD, and requiring mechanical ventilation	Organic lesion that could bleed (ie, an active gastroduodenal ulcer or a recent hemorrhagic CVA)
	Weight 45-100 kg	Severe liver failure leading to a decrease of the PT to < 50% (normal values 70%-100%)
		Severe renal impairment (serum creatinine > 300 μmol/L)
		Confirmed or uncontrolled hypertension (diastolic BP > 120 mm Hg)
		Congenital or acquired coagulation disorder
		History of hypersensitivity or thrombocytopenia to any type of heparin
		Contraindication to anticoagulant therapy, venography, or angiography
		Receiving any form of acetylsalicylic acid, ticlopidine, or oral anticoagulants
Leizorovicz et al,[9] PREVENT Study/2004	Age ≥ 40 y (mean ± SD age, 68.5 ± 11.7 y)	High risk of bleeding
	≤ 3 d of previous immobilization	Platelet count < 100×10^9/L
	Projected hospitalization ≥ 4 d	Hepatic insufficiency or active hepatitis
		Acute coronary syndrome within previous mo
		Bacterial endocarditis
		Immobilized lower limb due to cast or fracture
		Stroke within last 3 mo
		Major surgical or invasive procedure performed in previous mo or to be undertaken within next 2 wk
		Heparin or LMWH prophylaxis > 48 h before randomization
		Contraindication to heparin anticoagulation
		Creatinine > 2.0 mg/dL
	Acute medical illness: acute CHF (NYHA III-IV); or acute respiratory failure that did not require ventilatory support; or any of the following, if combined with ≥ 1 additional risk factor for VTE[b]: infection without septic shock, acute rheumatologic disorders, or inflammatory bowel disease	Pregnancy or breastfeeding
		Life expectancy < 1 mo

(Continued)

Table S1—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Mahe et al[10]/2005	Age > 40 y (mean age: treatment group, 76.1 y; placebo group 76.5 y	Systolic BP > 240 mm Hg, diastolic BP > 120 mm Hg
	Immobilized (unable to walk > 10 m alone)	Platelet level < 50,000/μm, TCA > control + 10 s
	Hospitalized < 24 h	PT < 50%
		Active gastroduodenal ulcer
		Renal failure (creatinine level > 300 μmol/L)
		Conditions requiring full-dose anticoagulation
		Stroke or major surgery within the previous 30 d
		Anticoagulant or antiplatelet therapy within last 7 d
	Acute medical illness: CHF (NYHA III-IV), acute or respiratory disease, nonpulmonary sepsis, cancer	Pregnancy
Lederle et al[11]/2006	Age ≥ 60 (mean ± SD age: treatment group, 71.3 y; placebo group, 72.1 y	Known thrombocytopenia (platelet count < 100,000/μm^3)
	Admitted or transferred to medical service	Systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg
		Occurrence within past 30 d of myocardial infarction, stroke, major surgery (defined as requiring general, spinal, or epidural anesthesia and lasting > 30 min), or any eye surgery
		Already receiving or requiring anticoagulation for reasons other than VTE prophylaxis
		Other contraindication to low-dose heparin
		Previous randomization into the study
	Predicted hospitalization ≥ 3 d	"Supportive/palliative care only" status

(Continued)

Table S1—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Cohen et al,[12] ARTEMIS Study/2006	Age ≥ 60 y (mean ± SD age: treatment group, 75.0 ± 8.3 y; placebo group, 74.4 ± 8.3 y)	High risk for bleeding
	Predicted immobilization ≥ 4 d	Serum creatinine level > 180 μmol/L in well-hydrated patient
	Hospitalized	Acute bacterial endocarditis
		Cerebral metastasis
		Recent hemorrhagic or ischemic stroke
		Brain, spinal, or ophthalmologic surgery
		Indwelling intrathecal or epidural catheter
		Anticipated intubation > 24 h
		Use of antithrombotics < 48 h before randomization
		Indication for anticoagulant prophylaxis or therapy
		Documented hypersensitivity to contrast media
	Acute medical illness: CHF (NYHA III-IV); or acute respiratory illness in the presence of chronic lung disease; or clinically diagnosed acute infections or inflammatory disorders, such as arthritis, connective tissue diseases, or inflammatory bowel disease	Life expectancy < 1 mo

aPTT = activated partial thromboplastin time; CVA = cerebrovascular accident; INR = international normalized ratio; LMWH = low-molecular-weight heparin; N/S = not stated as inclusion criterion; NYHA = New York Heart Association; PT = prothrombin time; TCA = trichloroacetic acid; UTI = urinary tract infection.

[a] Additional risk factors: age > 75 y, cancer, previous VTE, obesity (BMI ≥ 30 for men and ≥ 28.6 for women), varicose veins, hormone therapy (antiandrogen or estrogen, except for postmenopausal hormone-replacement therapy), and chronic heart or respiratory failure.

[b] Additional risk factors for VTE: age ≥ 75 y, cancer, previous VTE, obesity, varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of CHF, chronic respiratory failure, or myeloproliferative syndrome.

Table S2—*Observational Studies of Risk of VTE in Acutely Ill or Hospitalized Medical Patients*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Symptomatic VTE Events	No. (%) Cumulative Incidence [rate]
Bosson et al[13]/2006	Patients ≥ 40 y with an acute medical event, anticipated to have reduced mobility for at least 48 h (2002-2003)	1-28 d	Initiated in 35% of patients (n = 5,782)	DVT: confirmed by duplex ultrasonography	
				Overall	128 (0.77)
					[0.5 events/1,000 patient-days]
	Managed in the community (outpatients)			Treated: n = 4,163 (high risk: 1,664; low risk: 2,499)	77 (1.85)
	N = 16,532				High risk 42 (2.52)
					Low risk 35 (1.40)
				Untreated: n = 8,247 (high risk: 1,318; low risk: 6,843)	51 (0.62)
					High risk 16 (1.21)
					Low risk 35 (0.51)
				PE: confirmed by imaging	27 (0.2)
					[0.1 events/1,000 patient-days]
Darze et al[14]/2005	Patients with CHF (2001-2003)	Not reported	70% Received 40 mg enoxaparin	PE: confirmed by high-probability lung scintigraphy or positive spiral CT	
	N = 198			Overall	18 (9.1)
				Treated: n = 138	12 (8.7)
				Untreated: n = 60	6 (10.0)
Guijarro et al[15]/2005	All hospital inpatients (1998-2001)	Not reported	No information provided	DVT as the secondary diagnosis	5,559 (0.25)
	N = 2,228,894			PE as the secondary diagnosis at discharge	2,162 (0.1)
Kishimoto et al[16]/2005	All hospital inpatients (1987-1999)	Hospital stay: mean length of hospital stay not reported	Never or rarely used	DVT: diagnosed by venography or ultrasound	128 (0.1)
	N = 131,060	Time from admission to diagnosis (mean + SD): 21.3 + 21.2 d		PE: diagnosed by pulmonary perfusion scintigraphy and/or contrast-enhanced CT scan	41 (0.03)

(Continued)

Table S2—*Continued*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Symptomatic VTE Events	No. (%) Cumulative Incidence [rate]
Skaf et al[17]/2005	Ischemic or hemorrhagic stroke (1979-2003)	Until discharge	Not analyzed; authors assume most patients with ischemic stroke received antithrombotic therapy	DVT: method of diagnosis not reported	
		Mean length of hospital stay not reported		Overall	126,000 (0.8)
	N = 15,715,000			Ischemic stroke patients	104,000 (0.74)
	14,109,000 (ischemic), 1,606,000 (hemorrhagic)			Hemorrhagic stroke patients	22,000 (1.37)
				PE: method of diagnosis not reported	
				Overall	83,000 (0.53)
				Ischemic stroke patients	72,000 (0.51)
				Hemorrhagic stroke patients	11,000 (0.68)
Spyropoulos et al[18]/2011	IMPROVE registry patients: ≥ 18 y, admitted to the hospital for an acute medical illness, hospital stay ≥ 3 d (2002-2006)	Up to 3 mo	50% Received thromboprophylaxis (details provided in Tapson et al[19])	VTE: DVT and PE data not presented separately, or according to whether thromboprophylaxis was received	143 (0.9)
	N = 15,156				
Spyropoulos et al[20]/2011	Insured patients ≥ 40 y, hospitalized for cancer, CHF, severe infectious diseases, or lung diseases (2001-2005)	≥ 91 d (reported VTE by 30-d windows)	No information provided	VTE: discharge records	8,895 (5.6): 3,225 (36.3) events occurred in the first 30 d following hospitalization; 4,107 (46.2) events occurred > 3 mo postdischarge 6,300 (3.98) (DVT), 2,324 (1.47) (PE), 271 (0.17) (DVT/PE)
	N = 158,325			DVT: median time to DVT, 76 d	
				PE: median time to PE, 73 d	
				DVT/PE: median time to DVT/PE, 34 d	

(Continued)

Table S2—*Continued*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Symptomatic VTE Events	No. (%) Cumulative Incidence [rate]
Barbar et al[21]/2010	Patients ≥ 18 y admitted to a department of internal medicine (2007-2008) N = 1180	3 mo	186 (39.7%) of patients at high risk received appropriate prophylaxis; 52 (7.3%) of patients at low risk of VTE received prophylaxis	DVT: compression ultrasonography	
				Low risk: n = 711	0 (0)
				High risk: n = 469	22 (4.7)
				Treated: n = 186	3 (1.6)
				Untreated: n = 283	19 (6.7)
				PE: spiral CT or V̇/Q̇ scan	
				Low risk: n = 711	2 (0.3)
				Treated: n = 52	1 (1.9)
				Untreated: n = 659	1 (0.2)
				High risk: n = 469	13 (2.8)
				Treated: n = 185	1 (0.5) (nonfatal)
				Untreated: n = 283	12 (4.2) (11 nonfatal with or without DVT, 1 fatal PE)

Risk of symptomatic DVT in patients hospitalized for an acute medical event in studies reported here range from 0.1%-6.7%. The lowest estimate (0.1%) was derived from a study of hospitalized Japanese patients who are expected to have low rates based on previous reports in Japanese persons. The highest estimate (6.7%) was reported in the Barbar et al[21] study, which included 3 mo of follow-up and reported events within the treated and untreated groups. The next highest estimate (4.0%) was reported in the Spyropoulos et al[18,20] study, which also included 3 mo of follow-up but did not report by prophylaxis group. Excluding these three studies, rates ranged from 0.25%-0.8%. Rate of DVT was only reported in one study (Bosson et al) as 0.5 events/1,000 patient-days. Risk of PE in patients hospitalized for an acute medical event in studies reported here range from 0.03%-10%. The lowest estimate (0.03%) was derived from a study of hospitalized Japanese patients who are expected to have low rates based on previous reports in Japanese persons. The highest estimate (10%) was reported in the Darze et al[14] study, which reported events within the treated and untreated groups and only included patients with severe congestive heart failure who had high rates of traditional risk factors. The second highest estimate (4.2%) was reported in the Barbar et al[21] study, which included 3 mo of follow-up and reported events within the treated and untreated groups. Excluding these three studies, rates ranged from 0.1%-1.5%. Rate of PE was only reported in one study (Bosson et al[13]) as 0.1 event/1,000 patient-days. CHF = congestive heart failure; PE = pulmonary embolism; V̇/Q̇ = ventilation/perfusion.

Table S3—*RAMs for Predicting Symptomatic VTE in Medical Patients*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Description of RAM	Risk Strata	VTE No. (%)
Kucher et al[22]/2005	Hospitalized medical and surgical patients ≥ 18 y who were at increased risk for VTE (2000-2004)	3 mo	Prophylactic measures were ordered for 24% of patients in the study: 421 of the 1,255 patients in the intervention (electronic alerts) group (33.5%) and 182 of the 1,251 patients in the control group (14.5%)	Eight common risk factors used to determine each hospitalized patient's risk profile for VTE. Each risk factor was weighted according to a point scale:score of 3: cancer, prior VTE, and hypercoagulability; score of 2: major surgery; score of 1: advanced age, obesity, bed rest, and use of HRT or OC.	4	88 of 1,574 (5.6)
	Patients from neurology, newborn service, and the NICU were excluded, as were those receiving mechanical or pharmacologic prophylaxis.				> 4	76 of 932 (8.2)
	Part of an RCT to assess effectiveness of electronic alerts to improve the prescribing of appropriate thromboprophylaxis; N = 2,506			An increased risk of VTE was defined as a cumulative risk score of at least 4	Note: patients with a score < 4 were excluded from this study (they were not considered to be at increased risk for VTE)	
Khorana et al[23]/2008	Ambulatory patients ≥ 18 y with histologically confirmed diagnosis of cancer; required to be at the start of a new chemotherapy regimen, expected to complete four cycles of chemotherapy (2002-2005)	Median, 2.5 mo	Not reported	Score of 2: stomach, pancreatic cancer	Low (score 0)	0.8% and 0.3%
	N = 2,701 (derivation), 1,365 (validation)			Score of 1: lung, lymphoma, gynecologic, GU excluding prostate cancer; platelet count ≥ 350,000 μm, Hgb < 10 g/dL or use of ESA, leukocyte count > 11,000 μm, BMI ≥ 35	Intermediate (score 1-2)	1.8% and 2%
					High (score ≥ 3)	7.1% and 6.7% (risk of VTE in derivation and validation cohorts, respectively)

(Continued)

Table S3—*Continued*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Description of RAM	Risk Strata	VTE No. (%)
Barbar et al[21]/2010[b]	Consecutive patients ≥ 18 y admitted to a department of internal medicine (2007-2008)	3 mo	186 of 496 (39.7%) of patients at high risk received appropriate prophylaxis (the remaining 283 received none or inappropriate prophylaxis); 52 of 711 (7.3%) of patients at low risk of VTE received prophylaxis	Eleven common risk factors used to determine each hospitalized patient's risk profile for VTE. Each risk factor was weighted according to a point scale:	< 4 (low risk):	2 of 711 (0.3)
				Score of 3: active cancer, prior VTE, reduced mobility, known thrombophilic condition;	≥ 4 (high risk):	35 of 469 (7.5)
	Patients were excluded if they were on full-dose anticoagulation therapy, had contraindications to pharmacologic prophylaxis, or were pregnant			Score of 2: recent trauma and/or surgery	Received prophylaxis	4 of 186 (2.2)
	N = 1,180			Score of 1: age ≥ 70 y, heart and/or respiratory failure, acute MI or ischemic stroke, acute infection and/or rheumatologic disorder, obesity, ongoing hormonal treatment	Did not receive prophylaxis	31 of 283 (11.8)
				An increased risk of VTE was defined as a cumulative risk score of at least 4[c]		

(Continued)

Table S3—*Continued*

Study/Year	Patients	Duration of Follow-up	Use of Thromboprophylaxis	Description of RAM	Risk Strata	VTE No. (%)
Spyropoulos et al[18]/2011	IMPROVE study[19] patients aged ≥ 18 y, admission for an acute medical illness, ≥ 3 d hospitalization. First 10 eligible acutely ill hospitalized medical patients systematically enrolled at the start of each month at each hospital.	3 mo	Not reported	Two models developed: 4-factor model based on factors available at hospital admission and 7-factor model including factors available during hospital stay. Factor scores (1-3) based on logarithmic HR.	4-factor model: 0 (lowest risk)	24 of 4,981 (0.5)
					1	72 of 8,441 (1.0)
					2	20 of 1,166 (2.1)
					3	5 of 127 (4.0)
				4-factor model: older age and cancer, 1 point each; known thrombophilia and previous VTE, 3 points each.	4	16 of 376 (4.7)
					5-8 (highest risk)	6 of 65 (11)
	Patients excluded if enrolled in a therapeutic clinical trial or if any of the following applied: anticoagulant or thrombolytic drug use at admission or within 48 h after admission; major surgery or trauma ≤ 3 mo before admission; admission for DVT or PE (or diagnosis of either within 24 h of admission); follow-up deemed impossible.			7-factor model: older age, ICU/CCU stay, immobilization ≥ 7 d, 1 point each; current cancer, current LL paralysis, known thrombophilia, 2 points each; previous VTE 3 points.	7-factor model: 0 (lowest risk)	14 of 4,029 (0.4)
	N = 15,156				1	33 of 6,350 (0.6)
					2	31 of 2,420 (1.5)
					3	18 of 1,335 (1.6)
					4	30 of 729 (4.8)
					5-10 (highest risk)	17 of 262 (8.1)
					Not at ACCP risk	50 of 8,227 (0.7)
					At ACCP risk	93 of 6,898 (1.5)

ACCP = American College of Chest Physicians; CCU = critical care unit; ESA = erythropoiesis-stimulating agent; GU = genitourinary; Hgb = hemoglobin; HR = hazard ratio; HRT = hormone replacement therapy; LL = lower limb; MI = myocardial infarction; NICU = neonatal ICU; OC = oral contraceptive; RAM = risk assessment model; RCT = randomized controlled trial.

Other RAMs outlined in Spyropoulos[24] but excluded from the above table include one by Lutz et al,[25] which was regarded as "not thoroughly evidence-based or validated." Another RAM that was excluded from the table was that by Cohen et al,[12] which was not validated and assumed that all risk factors conferred a similar level of VTE risk. Another study excluded was a validation study by Bahl et al,[26] which used the Caprini RAM but was only assessed in surgical patients.

[a] An intervention study by Piazza et al[27] used the Kucher RAM to classify patients as at risk and therefore eligible for inclusion. Subjects included were those with a risk score ≥ 4 and the study found a cumulative risk of VTE of 3% in 90 d of follow-up.

[b] Barbar et al[8]: Not included in the Spyropoulos[24] review. The study validates the Padua Prediction Score in medical inpatients.

[c] Notes on Barbar et al[8] RAM: (1) active cancer: local or distant metastases and/or chemotherapy or radiotherapy in the previous 6 mo; (2) prior VTE: excludes superficial vein thrombosis; (3) reduced mobility: bed rest with bathroom privileges for at least 3 d; (4) recent trauma and/or surgery, ≤ 1 mo; (5) obesity: BMI ≥ 30.

Table S4—*[Section 2.3] Evidence Profile: Should Anticoagulant Prophylaxis (LMWH, UFH, Fondaparinux) vs Placebo/No Treatment Be Used in Hospitalized Medical Patients?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness[a]	Imprecision	Other Considerations	Anticoagulant Prophylaxis (LMWH, UFH, Fondaparinux)	Placebo/No Treatment[b]	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (follow-up 1-14 d)[c]												
4[c]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[e]	None	…	0.15%	RR, 0.47 (0.22-1)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	Moderate	Critical
								6.7%[e]		34 fewer per 1,000 (from 51 fewer to 0 fewer)		
Nonfatal PE (follow-up 1-22 d)[f]												
6[c,g]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[e]	None	…	0.15%	RR, 0.61 (0.23-1.67)[h]	1 fewer per 1,000 (from 1 fewer to 1 more	Moderate	Critical
								3.9%[e]		15 fewer per 1,000 (from 30 fewer to 26 more)		
Major bleeding (follow-up 10-110 d)												
8[e,i]	Randomized trials	No serious limitations	No serious inconsistency[j]	No serious indirectness	Serious[d]	None	25 of 4,301 (0.6%)	19 of 4,304 (0.4%)	OR, 1.32 (0.73-2.37)	1 more per 1,000 (from 1 fewer to 6 more)	Moderate	Critical

(Continued)

Table S4—*Continued*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness[a]	Imprecision	Other Considerations	Anticoagulant Prophylaxis (LMWH, UFH, Fondaparinux)	Placebo/No Treatment[b]	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 1-22 d)[f]												
5[c,k]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[l]	None	158 of 3,676 (4.3%)	165 of 3,679 (4.5%)	OR, 0.97 (0.79-1.19)	1 fewer per 1,000 (from 9 fewer to 8 more)	Moderate	Critical
Thrombocytopenia (follow-up 6-21 d)												
3[m]	Randomized trials	No serious limitations	No serious inconsistency[n]	No serious indirectness	Serious[d]	None	28 of 2,316 (1.2%)	31 of 2,308 (1.3%)	OR, 0.91 (0.54-1.53)	1 fewer per 1,000 (from 6 fewer to 7 more)	Moderate	Critical

Bibliography: Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: Anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med*. 2007;146(4):278-288. Lloyd NS, Douketis JD, Moinuddin I, Lim W, Crowther MA. Anticoagulant prophylaxis to prevent asymptomatic deep vein thrombosis in hospitalized medical patients: A systematic review and meta-analysis. *J Thromb Haemost*. 2008;6(3):405-414. Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). *Cochrane Database Syst Rev*. 2009;(3):CD003747. UFH = unfractionated heparin; RR = relative risk. See Table S1 and S2 legends for expansion of other abbreviations.

[a] For many of the trials, the ratio of patients screened to patients included was very high (eg, ≥ 100), raising some concerns about the overall representativeness of the trial populations.

[b] Baseline risk for DVT and PE (low-risk and high-risk populations) are derived from the RAM by Barbar et al.[8] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al).

[c] Data derived from Dentali et al. Studies sometimes reported outcomes for a longer duration of follow-up; however, the Dentali et al review only included outcomes during the on-treatment period.

[d] We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients) since it is difficult to obtain precise estimates in the absence of a sufficient number of outcomes.

[e] This estimate of the risk of the event in high-risk patients was derived from the Barbar et al[8] study, which stratified patients according to the Padua Prediction Score. The estimate shown reflects the risk among patients who did not receive prophylaxis (symptomatic DVT = 19 of 238, nonfatal PE = 11 of 283, fatal PE = 1 of 283).

[f] Fatal PE: seven RCTs, anticoagulants (14 of 9,902 [0.1%], control 39 of 10,051 [0.4%]; RR, 0.41 [0.22-0.76]; for low-risk patients: two fewer per 1,000 (from one fewer to three fewer) and for high-risk patients two fewer per 1,000 (from one fewer to three fewer). In four of the trials with available data there was fatal bleeding in 18 of 8,249 (0.22%) in the prophylaxis group vs seven of 8,365 (0.08%) in the placebo group.

[g] The Dentali et al review did not separate nonfatal and fatal PE; therefore, we went to the original studies to find which had reported nonfatal events only or both nonfatal and fatal events.

[h] The RR reported results from a meta-analysis using the DerSimonian-Laird random effects model. This model was chosen due to the number of studies (> 3) and because there was not a single study that dominated the meta-analysis.

[i] GI bleeding and intracranial bleeding were not routinely reported separately from major bleeding events in the individual component studies of the Dentali et al systematic review; however, at least one study (Cohen et al[12]) reported that GI bleeding events accounted for zero of two total and intracranial bleeding events accounted for zero of two total major bleeding events.

[j] There was some heterogeneity detected among individual studies; $I^2 = 30\%$.

[k] Although the Dentali et al review did not report fatal bleeding, some of the component studies did: two of nine bleeding outcomes in the treatment group and one of three in the placebo group of the Leizorovicz et al[20] study were fatal bleeding events. There were no fatal bleeding events in the Cohen et al[12] study (zero of two major bleeding outcomes). One of six bleeding outcomes in the treatment group and zero of four in the placebo group of the Samama et al[7] study were fatal bleeding events.

[l] Since the confidence interval ranges from a reduction in deaths to an increase in deaths, we are not assured that there is truly no effect.

[m] Data derived from the Alikhan and Cohen review.

[n] There was some heterogeneity detected among the individual studies; $I^2 = 42\%$.

Table S5—*Eligibility Criteria for RCTs of LDUH vs LMWH Thromboprophylaxis in Hospitalized Medical Patients*

Study/Year	Inclusion Criteria	Exclusion Criteria
Forette and Wolmark[28]/1995	Age N/S (mean age: 83 y)	Previous reduced mobility
	Recent transient reduced mobility	Existence of previous DVT, confirmed by echo Doppler 48 h prior to inclusion in study
	Hospitalized for > 4 wk	
	Acute medical illness	Previous DVT (within last 6 mo)
		Previous PE (within last y)
		Severe arterial hypertension
		Cerebral hemorrhage within previous 6 mo or any neurosurgical intervention
		Renal insufficiency
		Severe liver disease
		Surgical intervention (nonorthopedic 8 d; orthopedic 28 d)
		Receiving aspirin, ticlopidine, antiinflammatories, heparinoid, or vitamin K
		Contraindication to heparin, or venographic or angiographic investigations
Lechler et al,[29] PRIME/1996	Age > 18 y (mean age: 74 ± 13 y)	Bleeding disorder
	Expected immobilization > 1/2 daytime for whole study period (7 d)	Thrombocytopenia ($< 100{,}000 \times 10^9$/L)
	Hospitalized	Hemorrhagic stroke during the preceding 4 wk
	Acute medical illness plus ≥ 1 additional thromboembolic risk factor (> 60 y, malignancy, obesity, former thromboembolic event, cardiac insufficiency, paresis of the lower limbs, hemiplegia, paraplegia, or severe infection)	Head trauma in previous 6 mo
		Endocarditis
		Severe renal disease or renal insufficiency
		Thromboembolism
		Regional anesthesia
		Treatment with anticoagulants, antiplatelets or NSAIDs in the preceding 7 d
		Pregnancy and lactation
		Participation in clinical trial in preceding 6 wk

(Continued)

Table S5—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Bergmann and Neuhart,[30] EMSG/1996	Study participants were 65-80 y; mean age: enoxaparin group, 83.8 y; UFH group, 82.6 y	Ongoing venous, arterial or cardiac disease requiring anticoagulation
		Abnormal platelet count
	Reduced mobility	Renal disorders
	Hospitalized	Local disorders of the lower limb that would interfere with FUT
	Acute medical illness	Contraindication to anticoagulation
		History or allergy or thrombocytopenia induced by UFH or LMWH
		Any contraindication to isotopic or venographic investigations
Kleber et al[31]/2003	Age ≥ 18 y (mean age, 70 ± 14 y)	Immobilized > 24 h before enrollment
	Confined to bed for > 2/3 daytime	Acute signs of DVT or PE
	Hospitalized	Severe arterial hypertension
	Heart failure (NYHA III or IV; patients were allowed 100 mg daily of acetylsalicylic acid); or severe respiratory disease (characterized by impaired pulmonary function tests, blood gas analyses outside normal range, or both); and at least one additional pathologic condition: severe functional loss of ≥ 2 lung segments, severe secondary pulmonary hypertension, pneumonia, interstitial lung disease, lung cancer and/or metastases with a life expectancy > 2 mo, or exacerbation of COPD	Intracranial bleeding or hemorrhagic stroke in the preceding 6 mo
		Coagulation disorders
		GI ulcer
		Severe pancreatic, hepatic, or renal disease
		Advanced AIDS
		Ocular or central nervous system surgery in the preceding 4 wk
		Drug or alcohol abuse
		Patients taking anticoagulants/platelet inhibitors or NSAIDs
		Contraindications to LMWH or UFH therapy
		Allergy (unspecified)
		Hypersensitivity to contrast media

(Continued)

Table S5—*Continued*

Study/Year	Inclusion Criteria	Exclusion Criteria
Reiss et al,[32] CERTIFY/2010	Age > 70 y (mean ± SD age, 78.8 ± 6.3 y)	Immobilization > 3 d prior to randomization
	Significant decrease in mobility (bedridden or only able to walk short distances) expected for ≥ 4 d	Immobilization due to cast or fracture
	Hospitalized	Acute symptomatic DVT/PE
	Acute medical illness (infections and infestations, 28%; cardiac disorders, 22%; respiratory, thoracic, and mediastinal disorders, 17%; nervous system disorders, 7%; and so forth)	Uncontrolled hypertension
		Acute HIT-II or history of this
		Hemorrhagic stroke or intracranial bleeding (< 12 mo)
		Acute nonhemorrhagic stroke or history of this (< 3 mo)
		Acute or ongoing intracranial disease
		High risk of GI bleeding
		Acute endocarditis
		Known active retinopathy, or intravitreal or other intraocular bleeding
		Severe sepsis or need for ventilator support (continuous positive airway pressure, oxygen mask, and so forth, were permitted)
		Severe renal or liver disease
		Illness with very high acute mortality rate (> 30%)
		Spinal or epidural anesthesia or lumbar puncture within last 12 h
		Expected to undergo major surgical/invasive procedure within 3 wk following randomization
		Received LMWH/heparin for > 48 h in 5 d prior to randomization
		Indications for anticoagulation or thrombolysis
		Life expectancy < 6 mo

FUT = fibrinogen uptake; HIT-II = heparin-induced thrombocytopenia type 2; LDUH = low-dose unfractionated heparin; NSAIDs = onsteroidal antiinflammatory drugs. See Table S1 and S2 legends for expansion of other abbreviations.

Table S6—*[Section 2.4] Evidence Profile: Should Anticoagulant Prophylaxis With LMWH vs UFH Be Used in Hospitalized Medical Patients?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Anticoagulant Prophylaxis With LMWH	UFH	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (follow-up, 1-28 d)												
5[a]	Randomized trials	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	…	0.33%	RR, 0.77 (0.50-1.19)	1 fewer per 1,000 (from 2 fewer to 1 more)	Low	Critical
PE (follow-up, 1-28 d)												
5[a]	Randomized trials	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	…	0.20%	RR, 1.00 (0.28-3.59)	0 fewer per 1,000 (from 1 fewer to 5 more)	Low	Critical
Major bleeding												
5[a,d]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	11 of 2,795 (0.4%)	26 of 2,802 (0.9%)	RR, 0.48 (0.24-0.99)	5 fewer per 1,000 (from 0 fewer to 7 fewer)	Moderate	Critical
Mortality												
5[a,e]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	68 of 2,795 (2.4%)	77 of 2,805 (2.7%)	RR, 0.89 (0.65-1.23)	3 fewer per 1,000 (from 10 fewer to 6 more)	Moderate	Critical
Heparin-induced thrombocytopenia												
1	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c,f]	Reporting bias[g]	1 of 1,624 (0.06%)	2 of 1,615 (0.12%)	RR, 0.50 (0.05-5.48)	1 fewer per 1,000 (from 1 fewer to 1 more)	Low	Critical

Bibliography: Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). *Cochrane Database Syst Rev*. 2009;(3):CD003747. Reiss H, Haas S, Tebbe U, et al. A randomized, double-blind study of certoparin vs unfractionated heparin to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY Study. *J Thromb Haemost*. 2009;8(6):1209-1215. See Table S1, S2, and S5 legends for expansion of abbreviations.

[a] One study assessed UFH bid; four studies assessed UFH tid.

[b] The RR is derived from a mix of symptomatic and asymptomatic events and the baseline risk (risk with UFH) is derived from symptomatic events from the Riess et al study.

[c] We will consider the presence of serious imprecision when there are < 300 events in total (events in treatment and control patients), since it is difficult to obtain precise estimates in the absence of a sufficient number of outcomes.

[d] GI bleeding and intracranial bleeding were not routinely reported separately from major bleeding events in the individual component studies of the Alikhan and Cohen systematic review; however, one study (Lechler et al[29]) reported that GI bleeding events accounted for nine of 30 total major bleeding events, but number of events was not reported separately by treatment group.

[e] Fatal bleeding events not reported separately.

[f] Only one study (CERTIFY trial) reported this outcome and there were only three occurrences of thrombocytopenia overall; therefore, the suggestion of a protective effect of LMWH vs UFH is not well supported.

[g] Since only one study reported this outcome, it is possible that there was selective reporting of this outcome, which would indicate publication bias.

Table S7—*[Section 2.6] Evidence Profile: Should ASA or Other Antiplatelet Drugs Be Used in Hospitalized Medical Patients?*

Quality Assessment								Summary of Findings			
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA	With Placebo,[a] %	Relative Effect (95% CI)[b]	Absolute Risk Difference With ASA (95% CI)	Quality of Evidence	Importance
Symptomatic DVT (follow-up, 8 wk)											
1 RCT	No serious limitations	No serious limitations	Very serious limitations[c,d]	No serious limitations	Undetected	…	0.15	RR, 0.71 (0.52-0.97)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	Low	Important
						…	6.7		19 fewer per 1,000 (from 32 fewer to 2 fewer)		
PE (follow-up, 8 wk)											
64 RCTs[e]	No serious limitations	No serious limitations	Very serious limitations[c,d,f]	No serious limitations	Undetected	…	0.15	RR, 0.47 (0.37-0.59)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	Low	Critical
						…	3.9		21 fewer per 1,000 (from 25 fewer to 16 fewer)		
Mortality (follow-up, 35 d)											
1 RCT	No serious limitations	No serious limitations	Very serious limitations[c,d]	Serious limitations[g]	Undetected	…	4.5	RR, 0.97 (0.85-1.10)	1 fewer per 1,000 (from 7 fewer to 5 more)	Very low	Critical
Bleeding (follow-up, 35 d)											
1 RCT	No serious limitations	No serious limitations	Very serious limitations[c,d]	No serious limitations	Undetected	…	0.4	RR, 1.42 (1.16-1.74)[h]	2 more per 1,000 (from 1 more to 3 more)	Low	Important

Bibliography: Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet.* 2000;355(9212):1295-1302 (RCT report included a meta-analysis). MI, an important postoperative complication that can be impacted by ASA, is not reported in this evidence profile because it is not a relevant outcome in medical populations. An alternative approach to using indirect data from surgical patients is to only use data from medical patients included in the PEP trial report meta-analysis. Nine trials with a combined total population of 555 patients were conducted in high-risk medical patients (stroke, CHF, MI, or spinal cord injury). DVT events in these trials were asymptomatic and agents other than ASA were used in some trials. Antiplatelet agents were associated with reduced risk of asymptomatic DVT (RR, 0.65; 95% CI, 0.45-0.94), based on 39 of 261 vs 61 of 266 events, respectively. Results failed to show or to exclude a beneficial effect of antiplatelet agents on PE (RR, 0.38; 95% CI, 0.10-1.42), based on 3 of 275 vs 8 of 280 events, respectively). Bleeding and mortality rates were not reported. Using these data will give similar conclusion regarding DVT (significant reduction but low-quality evidence due to surrogacy of outcomes and imprecision) and will change conclusions regarding PE to become a non-statistically significant reduction with very-low-quality evidence due to severe imprecision and the indirectness caused by the baseline risk uncertainty. ASA = acetylsalicylic acid. See Table S1, S3, and S4 legends for expansion of other abbreviations.

[a] Baseline risk for DVT and PE (low-risk and high-risk populations) are derived from the RAM by Barbar et al.[21] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al).

[b] RRs in this evidence profiles are derived from the PEP trial publication. For PE, the meta-analysis included in PEP trial report is used, for DVT the meta-analysis was not used because it mainly included asymptomatic DVTs; instead, RR of symptomatic DVT events from PEP was used; for mortality and bleeding, PEP data were used because the meta-analysis did not pool these outcomes.

[c] Evidence is indirect because the relative effect is primarily derived from surgical patients (555 of the 26,890 patients included in PEP trial report meta-analysis were high-risk medical patients).

[d] DVT and PE baseline risk estimates are derived from an RAM derived in a cohort with a small number of outcome events, hence have uncertainty about them. This uncertainty can be labeled as imprecision or indirectness.

[e] Sixty-four RCTs consist of 63 from the meta-analysis published in the PEP trial report and the PEP trial.

[f] Some of the PE events in this meta-analysis may have been fatal.

[g] Wide CI that includes benefit and harm.

[h] RR of bleeding included the following bleeding events (fatal intracranial, extracranial, and GI bleeding events, and nonfatal melena and hematemesis, regardless of transfusion needs). Local bleeding events at the site of surgery were not considered as they are irrelevant to medical populations.

Table S8—*[Section 2.7.1] Evidence Profile: Should GCS vs No GCS Be Used in Hospitalized Medical Patients?*[a]

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	GCS	Control[a]	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (proximal or distal) (follow-up, 1-30 d; confirmed on imaging)												
1[b]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	…	0.15%	RR, 0.91 (0.63-1.29)	1 fewer per 1,000 (from 1 fewer to 1 more)	Moderate	Important
								6.7%		6 fewer per 1,000 (from 25 fewer to 19 more)		
PE (follow-up, 1-30 d; confirmed on imaging or autopsy)												
1[b]	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	…	0.15%	RR, 0.65 (0.33-1.31)	1 fewer per 1,000 (from 1 fewer to 1 more)	Low	Critical
								3.9%		14 fewer per 1,000 (from 26 fewer to 12 more)		
Mortality (follow-up, 30 d)												
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	131 of 1,321 (9.9%)	4.5%	RR, 1.06 (0.94-1.20)[d]	3 more per 1,000 (from 3 fewer to 9 more)	Moderate	Critical
Skin breaks/ulcers/blisters/skin necrosis (follow-up, 1-30 d; case-note review)												
1[b]	Randomized trials	Serious[e]	No serious inconsistency	Serious indirectness[b]	Serious[c]	None	64 of 1,256 (5.1%)	16 of 1,262 (1.3%)	RR, 4.02 (2.34-6.91)	38 more per 1,000 (from 17 more to 75 more)	Very low	Important
Lower limb ischemia/amputation (follow-up, 1-30 d; case-note review)												
1[b]	Randomized trials	Serious[e]	No serious inconsistency	No serious indirectness	Very serious[c]	None	7 of 1,256 (0.6%)	2 of 1,262 (0.2%)	RR, 3.52 (0.73-16.90)	4 more per 1,000 (from 0 fewer to 25 more)	Very low	Important

Bibliography: Kierkegaard A, Norgren L. Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. *Eur Heart J*. 1993;14(10):1365-1368. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stocking for prevention of deep-vein thrombosis after acute stroke. *QJM*. 2000;93(6):359-364. Dennis M, Sandercock PA, Reid J, et al. The CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicenter, randomized controlled trial. *Lancet*. 2009;373(9679):1958-1965. GCS = graduated compression stockings. See Tables S1 and S4 legends for expansion of other abbreviations.

[a] Baseline risk for DVT and PE (low-risk and high-risk populations) are derived from the RAM by Barbar et al.[21] Baseline risk for mortality and bleeding is derived from the control arm of medical patients in a meta-analysis (Dentali et al). Baseline risk for lower leg ischemia and skin breaks (derived from the control arms of CLOTS trial 1).

[b] Data from CLOTS trial 1 (stroke patients); hence, when results applied to medical patients, the quality of evidence should be downgraded due to indirectness

[c] For the outcomes of DVT and PE, imprecision refers only to the high-risk patients (estimates in low-risk patients are associated with very small absolute difference that is fairly precise). Imprecision otherwise is due to wide CI that includes appreciable benefit and harm and overall small number of events.

[d] The effect estimate shown here results from a fixed-effects meta-analysis of two trials of graduated compression stocking for prevention of DVT in hospitalized medical patients. The Muir trial reported death in nine of 65 patients with acute stroke in the treatment group and four of 32 patients in the control group. The CLOTS trial 1 reported death in 122 of 1,256 patients with acute stroke in the treatment group and 110 of 1,262 patients in the control group. Stockings were used for 1 week in two studies (Kierkegaard and Norgren; Muir et al) and until the patient was independently mobile, was discharged, refused to wear them, or developed skin problems in one study (Dennis et al). The largest of the studies, the CLOTS1 Trial conducted in 2,518 hospitalized stroke patients, was the only one to provide data on adverse effects of graduated compression stockings.

[e] Assessment of outcomes was based on case-note review and was not blinded to treatment allocation.

Table S9—*[Section 2.7.2] Evidence Profile: Should IPC Be Used in Hospitalized Nonsurgical Patients? Settings: Inpatients*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	IPC	Control,[a] %	Relative (95% CI)	Absolute	Quality of Evidence	Importance
Symptomatic DVT (follow-up, 30 d)												
19	Randomized trials	No serious limitations	No serious inconsistency	Serious indirectness[b]	No serious imprecision	None	…	0.15	RR, 0.43 (0.32-0.58)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	Moderate	Important
								6.7		38 fewer per 1,000 (from 46 fewer to 28 fewer)		
PE (follow-up, 30 d)												
8	Randomized trials	No serious limitations	No serious inconsistency	Serious indirectness[c]	Serious imprecision[d]	None	…	0.15	RR, 0.82 (0.41-1.62)	1 fewer per 1,000 (from 1 fewer to 1 more)	Low	Critical
								3.9		7 fewer per 1,000 (from 23 fewer to 24 more)		
Mortality (follow-up, 30 d)												
2	Randomized trials	No serious limitations	No serious inconsistency	Serious indirectness[e]	Serious imprecision[d]	None	…	4.5	RR, 1.03 (0.42-2.57)	1 more per 1,000 (from 76 fewer to 71 more)	Low	Critical
Skin complications (breaks, ulcers, blisters, and necrosis), not reported in any population[g]												
0	…	…	…	…	…	None	…	…	…	…		Important

Bibliography: Systematic review in surgical patients: Roderick P, Ferris G, Wilson K, et al. Toward evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anesthesia as thromboprophylaxis. *Health Technol Assess.* 2005;9(49):1-78. Systematic review in stroke patients: Naccarato M, Chiodo Grandi F, Dennis M, Sandercock PA. Physical methods for preventing deep vein thrombosis in stroke. *Cochrane Database Syst Rev.* 2010;(8): CD001922. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. *J Thromb Haemost.* 2010;8(11):2450-2457. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: Anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Internal Med.* 2007;146(4):278-288. IPC = intermittent pneumatic compression. See Tables S1, S3, and S4 for expansion of other abbreviations.

[a] Baseline risk for DVT and PE (low-risk and high-risk populations) are derived from the RAM by Barbar et al. Baseline risk for mortality is derived from the control arm of medical patients in a meta-analysis (Dentali et al).

[b] RR for DVT is derived from surgical patients (Roderick et al). Another element of indirectness is that DVT in these surgical patients was primarily asymptomatic DVT as ascertained by systematic Imaging tests. RR for proximal asymptomatic DVT was similar (0.52; 95% CI, 0.37-0.73). RR data are presented for IPC used as monotherapy because this is most relevant to the way IPCs are used in medical patients (ie, in patients who cannot receive anticoagulation). If IPCs are used alone or as adjunct to anticoagulant/antiplatelet therapy, RR is 0.49 (0.37-0.63), which leads to absolute effect per 1,000 patients of one fewer (from one fewer to one fewer) in low-risk patients and 32 fewer (from 42 fewer to 25 fewer) in high-risk patients.

[c] RR for PE is derived from surgical patients (Roderick et al). RR data are presented for IPC used as monotherapy because this is most relevant to the way IPCs are used in medical patients (ie, in patients who cannot receive anticoagulation). If IPCs are used alone or as adjunct to anticoagulant/antiplatelet therapy, RR is 0.77 (0.41-1.43). This does not change the conclusions of this evidence profile.

[d] CI includes negligible effect, appreciable benefit, and appreciable harm.

[e] RR is derived from RCTs in stroke (including one study of patients with hemorrhagic stroke). RCTs of IPCs in other populations did not measure or report mortality.

[f] Estimates for skin complications in medical patients using IPC are not available. Data from graduated compression stockings (section 2.3) may be indirectly considered.

Table S10—*Extended-Duration Prophylaxis in Hospitalized Medical Patients*

Study/Year	Title, Design	Patient Types	Excluded Patients	Intervention	Control	Outcomes	Results[a]	Length of Follow-up	Potential for Bias
Hull et al[33]/2010	Parallel RCT; N = 6,085	Acutely ill medical patients, ≥ 40 y with a life expectancy of at least 6 mo with recently reduced mobility for up to 3 d, defined as requiring total bed rest or being sedentary with (level 2) or without (level 1) bathroom privileges	Evidence of an active bleeding disorder	Subcutaneous enoxaparin, 40 mg/d for 28 ± 4 d	Placebo for 28 ± 4 d	VTE (composite of symptomatic proximal DVT, asymptomatic proximal DVT detected on mandatory bilateral compression ultrasound at end of double-blind treatment period, symptomatic PE, or fatal PE) during double-blind treatment period	VTE at 28 d	6 mo	Did not use ITT analysis: –For safety, only included those who has at least one dose of study drug (n = 5,963) –For efficacy, only included those who had at least one dose of study drug and had an evaluable ultrasonogram (n = 4,995)
							E: 61 of 2,485	For VTE:	
							P: 100 of 2,510	28 ± 4 d	
					After initial open-label, subcutaneous enoxaparin, 40 mg/d for 10 ± 4 d		Symptomatic proximal DVT	90 ± 10 d	
							E: 5 of 2,485	For death:	
			Major surgery within the previous 3 mo				P: 20 of 2,510	28 ± 4 d	
				After initial open-label, subcutaneous enoxaparin, 40 mg/d for 10 ± 4 d			Fatal PE	90 ± 10 d	
							E: 0 of 2,485		
							P: 1 of 2,510	180 ± 10 d	

(Continued)

Table S10—*Continued*

Study/Year	Title, Design	Patient Types	Excluded Patients	Intervention	Control	Outcomes	Results[a]	Length of Follow-up	Potential for Bias
							VTE at 90 d E: 65 of 2,485 P: 105 of 2,510 Mortality did not significantly differ at 30, 90, or 180 d		Conflict of interest: funder involved in data management, statistical analysis, and preparation of the article for publication
			Spinal or epidural analgesia or lumbar puncture within the previous 24 h						
			Known hypersensitivity to UFH, LMWH, or pork-derived products				Major bleeding		Did not report number of patients screened for inclusion
			History of heparin-induced thrombocytopenia or thrombosis			VTE incidence through 3 mo (day 90 ± 10)	E: 25 of 2,975 (4 intracranial; 1 fatal)		
						Mortality at 1 mo (day 28 ± 4), 3 mo (day 90 ± 10), and 6 mo (day 180 ± 10)	P: 10 of 2,988 (0 intracranial; 0 fatal)		Post hoc subgroup analyses
									Change in eligibility criteria part way through the trial and "data-driven"
		Following an amendment to the eligibility criteria, patients with level 2 immobility were required to have at least 1 VTE risk factor					Total bleeding E: 186 of 2,975		

(Continued)

Table S10—*Continued*

Study/Year	Title, Design	Patient Types	Excluded Patients	Intervention	Control	Outcomes	Results[a]	Length of Follow-up	Potential for Bias
			Participation in another clinical study within the previous 30 d				P: 116 of 2,988		
						Major bleeding[b] during and up to 48 h after double-blind treatment period	Serious adverse events		
							E: 216 of 2,975		
							P: 218 of 2,988		
			Persistent renal failure				HIT		
							E: 1 of 2,975		
			Known or suspected severe anemia of unexplained cause			Total (major and minor) bleeding events			
			A prosthetic heart valve			Serious adverse events (including thrombocytopenia)	P: 0 of 2,988		
			Cerebral metastases						
			Patients who are unlikely to be compliant				Post hoc analyses identified significant interaction between treatment effect and sex ($P = .016$) and age > 75 y ($P = .011$). Favorable risk-benefit ratio likely only for female patients with level 1 immobility > 75 y		
			Women who are breast-feeding, pregnant, or of childbearing age and not using effective contraception						
			Contraindications to pharmacologic anticoagulation						
			Use of LMWH or UFH at prophylactic doses for > 72 h prior to inclusion, or treatment with oral anticoagulant therapy within 72 h prior to enrollment						

ITT = intention to treat. See Table S1-S5 legends for expansion of other abbreviations.

[a] E = enoxaparin; P = placebo.

[b] Bleeding considered to be major if overt and associated with death; a decrease in hemoglobin level of at least 20 g/L, or a transfusion of at least 2 units of packed RBC or whole blood; surgical intervention; or retroperitoneal, intracranial, or intraocular bleeding.

Table S11—*[Section 2.8] Evidence Profile: Should Extended-Duration Thromboprophylaxis vs Standard Short-Duration Thromboprophylaxis Be Used for Prevention of VTE in Hospitalized Medical Patients With Reduced Mobility?*

Quality Assessment							Summary of Findings					
							No. (%) of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Extended-Duration Thromboprophylaxis	Standard Short-Duration Thromboprophylaxis	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic proximal DVT (follow-up, 24-32 d; bilateral compression ultrasonography or venography)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	None	None	5 of 2,485 (0.2)	20 of 2,510 (0.8)	RR, 0.25 (0.09-0.67)	6 fewer per 1,000 (from 3 fewer to 7 fewer)	Moderate	Critical
Fatal PE (follow-up, 24-32 d; autopsy)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	None[b]	None	0 of 2,485 (0)	1 of 2,510 (0)	RR, 0.34 (0.01-8.26)	0 fewer per 1,000 (from 0 fewer to 3 more)	Moderate	Critical
Mortality (follow-up, 24-32 d)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	60 of 2,975 (2)	65 of 2,988 (2.2)	RR, 1.00 (0.7-1.43)	0 fewer per 1,000 (from 7 fewer to 9 more)	Low	Critical
Major bleeding (follow-up, 24-34 d; hemorrhages considered to be major is they were overt and associate with death; a decrease in hemoglobin level of at least 20g/L or a transfusion of at least 2 units of packed RBC or whole blood; surgical intervention; or retroperitoneal, intracranial, or intraocular bleeding)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	None	None	25 of 2,975 (0.8)[c]	10 of 2,988 (0.3)[d]	RR, 2.51 (1.21-5.22)	5 more per 1,000 (from 1 more to 14 more)	Moderate	Critical
Serious adverse events (follow-up, 24-32 d[e]; New illness, worsening of preexisting illness, or study medication effects that resulted in death or persistent or substantial disability or incapability, were life-threatening or considered an important medical event, or required in-patient hospitalization or prolongation of existing hospitalization[f])												
1	Randomized trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	216 of 2,975 (7.3)	218 of 2,988 (7.3)	RR, 1.00 (0.83-1.19)	0 fewer per 1,000 (from 12 fewer to 14 more)	Low	Important
HIT (follow-up, 24-32 d[e])												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1 of 2,975 (0)	0 of 2,988 (0)	RR, 3.01 (0.12-73.93)	0 more per 1,000 (from 0 fewer to 0 more)	Very low	Critical

Bibliography: Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med.* 2010;153(1):8-18. See Table S1, S4, and S5 legends for expansion of abbreviations.

[a]Change in eligibility criteria part way through the trial and "data-driven"; did not use ITT analysis.

[b]We considered imprecision to be serious when CIs included appreciable benefit and harm. We considered imprecision very serious in the outcomes of fatal PE and HIT because the number of events was very small (1 and 2, respectively).

[c]Four intracranial, one fatal.

[d]Zero intracranial, zero fatal.

[e]The length of follow-up for this outcome was unclear from the published article.

[f]Includes 13 VTEs, one in enoxaparin, 12 in placebo group; includes 20 major bleeding events, 15 in enoxaparin group, five in placebo group.

Table S12—*Prognostic Factors Associated With VTE in ICU Patients*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Comments
			Studies using multivariable analysis				
Shorr et al[34]/2009	Multicenter RCT (XPRESS)	1,935 sepsis patients receiving DAA	LMWH (Enoxaparin 40 mg SC od), UFH 5,000 International Units SC bid or placebo during DAA infusion period	DVT screening with ultrasound between days 4-6	28 d	RR older patients (age > 75 y), 1.92 (95% CI, 1.22-3.04; $P = .004$); history of VTE, 4.6 (2.17-9.79, $P < .001$); multivariable analysis: history of VTE; OR, 3.66 (95% CI, 1.77-7.56; $P = .005$)	Multivariable analysis adjusted for age, recent surgery, history of VTE, baseline heparin, use of vasopressors, need for mechanical ventilation
Cook et al,[35] DIRECT/2008	Multicenter prospective cohort	138 medical-surgical ICU patients with renal insufficiency	Dalteparin 5,000 International Units SC od	DVT screening with ultrasound on admission and twice weekly	Up to 30 d	Elevated APACHE II score; HR for 10-unit increase, 2.25 (95% CI, 1.03-4.91)	Independent variables: baseline VTE risk factors,[a] transfusion, CVC, inotrope or vasopressor, mechanical ventilation
Cook et al,[36] VETEC/2005	Single-center prospective cohort	261 medical-surgical ICU patients	Dalteparin 5,000 International Units SC od	DVT screening with ultrasound on admission and twice weekly		Personal or family history of VTE, HR, 4.0 (95% CI, 1.5-10.3); end-stage renal failure, HR, 3.7% (1.2%-11.1%); platelet transfusion, HR, 3.2% (1.2%-8.4%); vasopressor use, HR, 2.8% (1.1%-7.2%)	Independent variables: baseline VTE risk factors, exposures within 2 wk and during ICU admission, daily ICU exposures[b]
Ibrahim et al[37]/2002	Prospective cohort	110 medical ICU patients requiring mechanical ventilation > 7 d	Screening duplex ultrasound of upper and lower extremities every 7 d	DVT, mortality; also hospital and ICU LOS, duration of mechanical ventilation	N/S (while in ICU)	Duration of CVC placement (1-d increments), RR of DVT, 1.04 (95% CI, 1.03-1.05; $P < .001$)	Cox proportional hazards model
Kollef[38]/1998	Single-center prospective cohort	323 medical ICU patients	Semiquantitative d-dimer	VTE (not systematically screened)	N/S (while in ICU)	Increased d-dimer independently associated with vascular thrombosis, adjusted OR, 5.06 (95% CI, 2.96-8.65; $P = .003$)	Multiple logistic regression

Studies that used univariate analysis to identify risk factors for VTE were not included in the table.[34,39] APACHE = Acute Physiology and Chronic Health Evaluation; CVC = central venous catheter; DAA = drotrecogin alfa (activated); LOS = length of stay; od = once daily; SC = subcutaneous. See Table S2, S4, S5, and S7 legends for expansion of other abbreviations.

[a] Baseline risk factors: personal or family history, known thrombophilic disorder, current or recent (within 5 y) malignancy.

[b] Baseline VTE risk factors: age; gender; BMI; admission diagnosis; medical or surgical status; APACHE II score; pre-ICU location; personal or family history of VTE; known thrombophilic disorder; active or previous malignancy; chronic cardiac, respiratory, renal, or CNS disease; smoking; hospitalization within 6 mo; surgery within 12 wk; bed rest of ≥ 3 d in prior 4 wk; activity level. Exposures within 2 wk before ICU admission and daily thereafter included CVCs, subcutaneous UFH, UFH for catheter patency, therapeutic UFH or LMWH, warfarin ASA, NSAIDS, antiplatelet drugs, vitamin K, transfusion (RBC, plasma, platelets, cryoprecipitate). Daily ICU variables included vasopressors, mechanical ventilation, positive end-expiratory pressure, dialysis, surgical interventions, Multiple Organ Dysfunction score, hemoglobin, platelet count, INR, aPTT, IV sedatives/opiates/paralytics.

Table S13—*Description of Studies of Prophylactic Anticoagulation in ICU Patients*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Comments
				UFH vs Placebo			
Cade[40]/1982	Single-center RCT	119 medical-surgical ICU patients	UFH 5,000 International Units SC bid vs placebo	DVT detected by fibrinogen leg scanning for median 7 d (4-10 d)	Not specified (while in ICU)	DVT: UFH, 13% vs placebo 29%; $P < .05$	57% Distal DVT, 1/3 bilateral, 1/5 proximal
				LMWH vs Placebo			
Fraisse et al[8]/2000	Multicenter, double-blind RCT	223 mechanically ventilated patients with COPD	LMWH (nadroparin ~65 International Units/kg SC od) vs placebo	DVT (detected by venography before day 21), bleeding, mortality	Up to 21 d	DVT: LMWH, 13 of 84 (15.5%) vs placebo, 24 of 85 (28.2%); $P = .045$ Major bleeding: LMWH, 6 of 108 (5.5%) vs placebo, 3 of 113 (2.7%); $P = .28$ Mortality: LMWH, 8 of 84 (9.5%) vs placebo, 8 of 85 (9.4%)	Weekly ultrasound; proximal DVT in 3 of 13 LMWH and 7 of 24 placebo

(Continued)

Table S13—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Comments
LMWH vs UFH							
PROTECT investigators[41]/2011	Multicenter, double-blind RCT	3,764 critically ill patients expected to remain in ICU for ≥ 3 d	LMWH (dalteparin 5,000 International Units SC od) vs UFH 5,000 International Units SC bid	Proximal DVT (detected by compression ultrasound ≥ 3 d after randomization; compression ultrasound performed within 2 d of admission, twice weekly, and as clinically indicated); secondary outcomes: any DVT, PE, VTE, death, major bleeding, HIT	While in ICU	Proximal DVT: LMWH, 96 of 1,873 (5.1%) vs UFH, 109 of 1,873 (5.8%); HR, 0.92 (95% CI, 0.68-1.23; *P* = .57) Any DVT: LMWH, 138 of 1,873 (7.4%) vs UFH, 161 of 1,873 (8.6%); HR, 0.93 (95% CI, 0.72-1.19; *P* = .54) PE: LMWH, 24 of 1,873 (1.3%) vs UFH, 43 of 1,873 (2.3%); HR, 0.51 (95% CI, 0.30-0.88; *P* = .01) VTE: LMWH, 154 of 1,873 (8.2%) vs UFH, 186 of 1,873 (9.9%); HR, 0.87 (95% CI, 0.69-1.10; *P* = .24) Death (ICU): LMWH, 284 of 1,873 (15.2%) vs UFH, 304 of 1,873 (16.2%); HR, 0.97 (95% CI, 0.82-1.15; *P* = .71) Major bleeding: LMWH, 103 of 1,873 (5.5%), UFH, 105 of 1,873 (5.6%) HIT: LMWH, 5 of 1,873 (0.3%) vs UFH, 12 of 1,873 (0.6%)	All DVT outcomes were screened for by ultrasound; PE was not screened for, but was clinically suspected and classified as possible, probable, or definite

(Continued)

Table S13—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results	Comments
Shorr et al[34]/2009	Multicenter RCT (XPRESS)	1,935 sepsis patients receiving DAA	LMWH (enoxaparin 40 mg SC od), UFH 5000 International Units SC bid or placebo during DAA infusion period	DVT (detected by compression ultrasound between days 4-6)	28 d	VTE: LMWH, 23 of 478 (5.9%), UFH, 26 of 498 (6.3%), placebo, 56 of 959 (5.8%) PE: LMWH, 4 of 478 (0.4%), UFH, 2 of 498 (0.4%), placebo, 8 of 959 (0.8%)	Most DVT clinically silent
De et al[42]/2010	Single-center RCT	N = 156, critically ill surgical patients undergoing major surgery	LMWH (enoxaparin 40 mg od) vs UFH 5,000 International Units SC bid	DVT (detected with Doppler between postoperative days 5-7 and clinical suspicion), bleeding, mortality	~6 wk	DVT: LMWH, 1 of 81 (1.2%) vs UFH, 2 of 75 (2.7%), Major bleeding: LMWH, 1 of 81 (1.2%) vs UFH, 2 of 75 (2.7%) Mortality: LMWH, 9 of 81 (11%) vs 6 of 75 (8%)	Cause of death not VTE or bleeding No screening ultrasound, Doppler only
Single-arm clinical studies using LMWH/UFH							
Douketis et al[43]/2008	Multicenter, single-arm clinical trial	138 critically ill medical-surgical patients with severe renal insufficiency (CrCl < 30 mL/min)	LMWH (dalteparin 5,000 International Units SC od) until ICU discharge or 30 d	DVT (detected by twice-weekly screening ultrasound), bleeding	Until ICU discharge or up to 30 d	DVT: 7 of 138 (5.1%; 95% CI, 2.5%-10.1%) Major bleeding: 10 of 138 (7.2%; 95% CI, 4.0%-12.8%)	All DVT asymptomatic and proximal; 6 of 7 associated with femoral catheters
Rabbat et al[44]/2005	Single-center prospective cohort	19 critically ill medical-surgical patients with CrCl > 0 mL/min	LMWH (dalteparin 5,000 International Units SC od)	VTE (twice weekly screening ultrasound), bleeding	Median 12 d (4-54 d)	VTE: 1 of 19 (5.3%) Bleeding: 2 of 19 (10.5%)	1 Internal jugular vein thrombosis, 1 major and 1 minor bleeding
Cook et al[36]/2005	Single-center prospective cohort	261 medical-surgical ICU patients	UFH 5,000 International Units SC bid	DVT detected by compression ultrasound on admission and twice weekly	Until ICU discharge, death or development of DVT	Incident DVT: 25 of 261 (9.6%; 95% CI, 6.3%-13.8%)	Most DVT asymptomatic (not clinically suspected)

CrCl = creatinine clearance. See Table S1-S5 and S11 legends for expansion of other abbreviations.

Table S14—*[Section 3.4.1] Evidence Profile: Should UFH vs Placebo Be Used for DVT Prevention in Critically Ill Adult Patients?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	UFH	Placebo	Relative (95% CI)	Absolute	Quality
Symptomatic DVT (up to 28 d)[a] (important outcome)											
1	RCT	None	None	None	Serious[b]	None	26 of 498 (5.22%)	56 of 959 (5.84%)	RR, 0.89 (0.57-1.41)	6 fewer per 1,000 (from 25 fewer to 24 more)	Moderate
Symptomatic PE (up to 28 d)[a] (important outcome)											
1	RCT	None	None	Serious[a]	Serious[b]	None	…	4.2%	RR, 0.48 (0.10-2.26)	22 fewer per 1,000 (from 38 fewer to 53 more)	Low
Mortality (critical outcome)											
No data	…	…	…	…	…	…	…	…	…	…	…
Major bleeding (important outcome)											
No data	…	…	…	…	…	…	…	…	…	…	…

Bibliography: Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost.* 2009;101(1):139-144. See Table S1 and S4 legends for expansion of abbreviations.

[a] Symptomatic DVT was reported in Shorr and Williams, symptomatic PE was not reported. Therefore, we estimated PE baseline risk from observational studies (4.2%) and used RR from Shorr and Williams, which was likely a mix of symptomatic and asymptomatic events.

[b] Small number of patients and small number of events in each group; CI include benefit and harm.

Table S15—*[Section 3.4.2] Evidence Profile: Should LMWH vs Placebo Be Used for DVT Prevention in Critically Ill Adult Patients? Setting: ICU*

Quality Assessment							Summary of Findings					
							No. of Patients (%)		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	LMWH	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (5-28 d)[a]												
1	RCT	No serious limitations[b]	None[c]	None	Serious[d]	None	23 of 478 (4.81%)	56 of 959 (5.84%)	RR, 0.82 (0.51-1.32)	9 fewer (from 24 fewer to15 more)	Moderate	Important
Symptomatic PE (5-28 d)[a]												
1	RCT	No serious limitations[b]	None[c]	Serious[a]	Very serious[d]	None	…	4.2[e]	RR, 1.01, (0.31-3.31)	0 fewer (from 29 fewer to 97 more)	Very low	Important
Major bleeding (follow-up mean, 11.6 d)												
1	RCT	No serious limitations[b]	None[c]	No serious indirectness	Very serious[d]	None[f]	6 of 108 (5.6%)	3 of 113 (2.7%)	RR, 2.09 (0.54 to 8.16)	29 more per 1,000 (from 12 fewer to 190 more)	Very low	Important
Mortality (follow-up mean, 11.6 d)												
1	RCT	No serious limitations[b]	None[c]	No serious indirectness	Very serious[d]	None[ff]	8 of 84 (9.5%)	8 of 85 (9.4%)	RR, 1.01 (0.4 to 2.57)	1 more per 1,000 (from 56 fewer to 148 more)	Very low	Critical

Bibliography: Fraisse F, Holzapfel L, Couland JM 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(4 pt 1):1109-1114. Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*. 2009;101(1):139-144. See Table S1-S4, S10, and S11 legends for expansion of abbreviations.

[a] Symptomatic DVT was reported in Shorr and Williams symptomatic PE was not reported in Shorr et al (zero events in both study arms by Fraisse et al). Therefore, we estimated PE baseline risk from observational studies (4.2%) and used RR from Shorr and Williams, which was likely a mix of symptomatic and asymptomatic events.

[b] Both studies double-blind, ITT analysis. Fraisse et al: venography could not be performed in 52 of 221 (23.5%) of patients; these patients were excluded from the efficacy analysis. Shorr and Williams: study assessed efficacy of prophylactic doses of LMWH/UFH in patients with severe sepsis only while receiving drotrecogin alfa. Fraisse et al: study supported by a grant from Sanofi (manufacturer of nadroparin).

[c] Clinical heterogeneity of the trials: (1) Fraisse et al: Nadroparin dosed according to weight (3,800 units for 45-70 kg; 5,700 units for 71-110 kg); Shorr and Williams: enoxaparin 40 mg SC od; (2) Fraisse et al: Patients with COPD exacerbation requiring mechanical ventilation; Shorr and Williams: 1,935 sepsis patients receiving drotrecogin alfa; (3) Method of DVT assessment: Fraisse et al: venography at end of study period (max 21 ± 1 d); Shorr and Williams: compression ultrasonography between days 4 and 6; and (4) Fraisse et al: results from Doppler ultrasonography and venography was discrepant, but no further information was provided. Venography (at the end of the study period) was used to assess efficacy in this study, but ultrasonography was performed before inclusion and weekly.

[d] Small number of patients and small number of events in each group; CI include benefit and harm. The RR of the outcome of PE is considered very imprecise due to small number of events (4 of 478 LMWH vs 8 of 959 placebo).

[e] No direct evidence regarding symptomatic PE. Therefore, we estimated baseline risk from observational studies (4.2%) and used RR from Shorr and Williams, which was likely a mix of symptomatic and asymptomatic events.

[f] Major bleeding and mortality were only assessed in Fraisse et al (adjudicated by independent committee). Bleeding was defined as overt, associated with decrease in Hgb of > 2 g/dL, packed RBC transfusion, retroperitoneal or intracranial or resulted in discontinuation of prophylaxis. Mortality was mainly due to cardiovascular complications associated with infection (not due to bleeding).

Table S16—*[Section 3.4.3] Evidence Profile: Should Any Heparin (LDUH or LMWH) vs Placebo Be Used for DVT Prophylaxis in Critically Ill Adult Patients?*

Quality Assessment							Summary of Findings					
							No. of Patients (%)		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	LMWH or LDUFH[a]	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (5-28 d)[b]												
1	RCT	No serious limitations[c]	None	None	Serious[d]	None	49 of 976 (5.0%)	56 of 959 (5.8%)	RR, 0.86 (0.59-1.25)	4 fewer per 1,000 (from 12 fewer to 8 more)	Moderate	Important
Symptomatic PE (5-28 d)[e]												
1	RCT	No serious limitations[c]	None	Serious[e]	Serious[d]	None	…	4.2%	RR, 0.73 (0.26- 2.11)	11 fewer per 1,000 (from 31 fewer to 47 more)	Low	Important
Major bleeding (follow-up mean, 11.6 d)[f]												
1	RCT	No serious limitations[c]	None	No serious indirectness	Very serious[d]	None[f]	6 of 108 (5.6%)	3 of 113 (2.7%)	RR, 2.09 (0.54 to 8.16)	29 more per 1,000 (from 12 fewer to 190 more)	Very low	Important
Mortality (follow-up mean, 11.6 d)[f]												
1	RCT	No serious limitations[c]	None	No serious indirectness	Very serious[d]	None[f]	8 of 84 (9.5%)	8 of 85 (9.4%)	RR, 1.01 (0.4 to 2.57)	1 more per 1,000 (from 56 fewer to 148 more)	Very low	Critical

Bibliography: Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*. 2009;101(1):139-144. Fraisse F, Holzapfel L, Couland JM, 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(4 pt 1):1109-1114. See Table S1-S5 and S11 legends for expansion of abbreviations.

[a] Includes LMWH (enoxaparin 40 mg od, nadroparin based on weight od) and unfractionated heparin 5,000 units bid.

[b] Data are only available on symptomatic DVT from Shorr and Williams.

[c] We did not rate evidence down for methodological limitations or inconsistency, although there were some possible deficiencies in these areas. Shorr and Williams: prophylaxis following 6 d was left to the discretion of the physician; Fraisse et al and Cade: unclear description of randomization and allocation concealment, and there may be possible clinical (not statistical) heterogeneity in the patient populations: sepsis patients receiving drotrecogin alfa (Shorr and Willimas), patients with COPD requiring ventilation (Fraisse et al), general ICU (Cade); and in the methods of DVT ascertainment: compression ultrasound (Shorr and Williams), venography (Fraisse et al); ^{125}I fibrinogen leg scanning (Cade); Shorr and Williams: 28-d treatment period; Fraisse et al: 11.6-d mean duration of treatment; Cade: 7.7 mean days of leg scanning.

[d] Relatively small number of patients and small number of events in each group; CIs include benefit and harm.

[e] No direct evidence regarding symptomatic PE. Therefore, we estimated PE baseline risk from observational studies (4.2%) and used RR from Shorr and Williams, which was likely a mix of symptomatic and asymptomatic events.

[f] Major bleeding and mortality were only assessed in Fraisse et al.

Table S17—*[Section 3.4.4] Evidence Profile: Should LMWH vs UFH Be Used for DVT Prevention in Critically Ill Adult Patients?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies[a]	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	LMWH	UFH	Relative (95% CI)	Absolute	Quality	Importance
Symptomatic DVT (follow-up 7-28 d)[b]												
2	RCT	None[c]	No serious inconsistency	None	Serious[d]	None	51 of 2,351 (2.2%)	60 of 2,371 (2.5%)	RR, 0.87 (0.60-1.25)[e]	3 fewer per 1,000 (from 10 fewer to 6 more)	Moderate	Important
Symptomatic PE (follow-up 7-28 d)												
1	RCT	None[c]	No serious inconsistency	None	Serious[d]	None	22 of 1,873 (1.2%)	38 of 1,873 (2.0%)	RR, 0.58 (0.34-0.97)	8 fewer per 1,000 (13.2 fewer to 0.6 fewer)	Moderate	Important
Major bleeding (follow-up 7-47 d)												
2[f]	RCT	None[c]	No serious inconsistency	None	Serious[d]	None	104 of 1,954 (5.3%)	107 of 1,948 (5.5%)	RR, 0.97 (0.75-1.26)[e]	2 fewer per 1,000 (from 14 fewer to 14 more)	Moderate	Important
Mortality (follow-up 7-47 d)												
2	RCT	None[c]	No serious inconsistency	None	Serious[d]	None	293 of 1,954 (15.0%)	310 of 1,948 (15.9%)	RR, 0.94 (0.81-1.09)[e]	10 fewer per 1,000 (from 30 fewer to 14 more)	Moderate	Critical
HIT (7 d)												
1	RCT	None[c]	No serious inconsistency	None	Serious[d]	None	5 of 1,873 (0.3%)	12 of 1,873 (0.6%)	RR, 0.42 (0.15-1.18)	3 fewer per 1,000 (from 5 fewer to 1 more)	Moderate	Important

Bibliography: PROTECT Investigators. Dalteparin vs unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305-1314. Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost.* 2009;101(1):139-144. De A, Roy P, Garg VK et al. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. *Blood Coagul Fibrinolysis*. 2010;21(1):57-61. IQR = interquartile range. See Table S1-S5 and S11 legends for expansion of other abbreviations.

[a] The outcome of symptomatic PE was reported in PROTECT and the outcome of symptomatic DVT was reported in PROTECT and Shorr and Williams studies. The outcomes of bleeding and mortality were reported in PROTECT and De et al studies. The outcome of HIT was reported in PROTECT. The interventions were: PROTECT: dalteparin 5,000 International Units SC od; Shorr and Williams and De et al: enoxaparin 40 mg SC od; UFH 5,000 units SC bid; and all studies included placebo injection. PROTECT: compression ultrasound performed within 2 d of ICU admission then twice weekly while in ICU; Shorr and Williams: compression ultrasound performed between day 4 and 6 of drotrecogin alfa treatment; De et al: Doppler performed between postoperative day 5 and 7. Population: PROTECT: 3,764 patients expected to remain in ICU at least 3 d; Shorr and Williams: 1,935 sepsis patients receiving drotrecogin alfa; De et al: 156 patients undergoing major surgery requiring at least 24 h in ICU.

[b] PROTECT: Median duration of study period: 7 d (IQR 4-12 d); Shorr and Williams: 28-d study period; De et al: Median follow-up: 47 d.

[c] De et al: Unclear description of randomization process, blinding, and losses to follow-up. PROTECT had adequate bias protection measures.

[d] Relatively small number of events and wide CIs that include benefit and harm.

[e] Fixed effect model used for meta-analysis.

[f] Major bleeding definition: PROTECT: hemorrhage at a critical site, bleeding resulting in need for therapeutic intervention, causing hemodynamic compromise, requiring 2 units transfusion or resulting in death. De et al: GI bleeding diagnosed on stool testing or upper GI endoscopy or any bleeding episode requiring reoperation.

Table S18—*[Section 4.2] Evidence Profile: Should Heparin vs No Heparin Be Used in Patients With Cancer Who Have No Other Therapeutic or Prophylactic Indication for Anticoagulation?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Heparin	No Heparin, %	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up, 12 mo)[a]												
8	Randomized trials	No serious limitations[b]	Serious[c]	No serious indirectness	No serious imprecision[d]	None	735 of 1,464 (50.2%)	64.9[e]	RR, 0.93 (0.85-1.02)	45 fewer per 1,000 (from 97 fewer to 13 more)	Moderate	Important
Symptomatic VTE (follow-up, 12 mo)												
7	Randomized trials	No serious limitations[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	38 of 1,338 (2.8%)	2.9[e]	RR, 0.55 (0.37-0.82)	13 fewer per 1,000 (from 5 fewer to 18 fewer)	High	Critical
Major bleeding (follow-up, 12 mo)												
9	Randomized trials	No serious limitations[b]	No serious inconsistency	No serious indirectness	Serious[f]	None	30 of 1,624 (1.8%)	0.7[b]	RR, 1.3 (0.59-2.88)	2 more per 1,000 (from 3 fewer to 13 more)	Moderate	Important
Minor bleeding (follow-up, 12 wk)												
7	Randomized trials	No serious limitations[b]	No serious inconsistency	No serious indirectness	Serious[f]	None	85 of 1,365 (6.2%)	2.7[e]	RR, 1.05 (0.75-1.46)	1 more per 1,000 (from 7 fewer to 12 more)	Moderate	Not important
Health-related quality of life (follow-up, 12 mo; the Uniscale and the Symptom Distress Scale; better indicated by lower values)												
1	Randomized trials	Serious[g]	No serious inconsistency	No serious indirectness	Serious[g]	None			Not estimable[h]		Low	Important

Bibliography: Akl EA, Gunukula SK, van Doormaal FF, et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database Syst Rev*. 2011;(4)CD006652. See Table S4 legend for expansion of abbreviation.

[a]The outcomes are reported at 12-mo follow-up. Mortality at 2-y follow-up increases from 65% to 86%.

[b]Vast majority of studies had allocation concealment and used blinded outcome and adjudication. We did not downgrade, although there was some concern about lack of blinding in some studies; the overall risk of bias was believed to be very low.

[c]There is moderate heterogeneity among studies included in the analysis of death at 12 mo ($I^2 = 41\%$). The subgroup analysis for mortality at 12 mo was statistically significant and suggested survival benefit in patients with small cell lung cancer but not in patients with advanced cancer. Overall we decided to downgrade by one level when considering these issues along with imprecision.

[d]CI interval includes effects suggesting benefit as well as no benefit.

[e]Baseline risk is the median of risk in control groups of trials included in the systematic review.

[f]CI includes possibility of both harms or benefits.

[g]High risk of bias and only 138 patients enrolled.

[h]The scores for the two scales were similar for the two study groups, both at baseline and at follow-up.

Table S19—*[Section 4.3] Evidence Profile: Should Oral Anticoagulation Be Used in Patients With Cancer With No Therapeutic or Prophylactic Indication for Anticoagulation?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Oral Anticoagulation	Control, %	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up median, 1 y)												
5	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	360 of 801 (44.9%)	64.9[b]	RR, 0.94 (0.87-1.03)	39 fewer per 1,000 (from 84 fewer to 19 more)	Moderate	Important
Symptomatic VTE (follow-up, 1 y)												
1	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	1 of 154 (0.6%)	2.9[b]	RR, 0.15 (0.02-1.2)	25 fewer per 1,000 (from 28 fewer to 6 more)	Moderate	Important
Major bleeding (follow-up, median 1 y)												
4	Randomized trials	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	72 of 650 (11.1%)	0.7[b]	RR, 4.24 (1.85-9.68)	23 more per 1,000 (from 6 more to 61 more)	Moderate	Important
Health-related quality of life: not reported												
0	…	…	…	…	…	None	0 of 0 (0%)	0	…	…		Important

Bibliography: Akl EA, Vasireddi S, Gunukula S, et al. Oral anticoagulation for prolonging survival in patients with cancer. *Cochrane Database Syst Rev*. 2010;(12):CD006466.

[a]We downgraded because lack of blinding of patients and providers in four out of five studies; it was unclear whether allocation was concealed in two studies; and only one study clearly used ITT analysis. All studies used warfarin at a dose to increase PT 1.5 to 2 times (four studies) or to keep INR between 1.3 and 1.9. See Tables S4 and S10 legends for expansion of abbreviations.

[b]Baseline risk is the median of risk in control groups of trials included in a systematic review of the effects of parenteral anticoagulation in patients with cancer but no prophylactic or therapeutic indication for anticoagulation (Akl et al).

[c]We downgraded because the precision of the estimate does not exclude a patient important benefit (the lower limit of RR still suggests a benefit that might be relevant given the high baseline risk).

[d]We downgraded because lack of blinding of patients and providers in three out of four studies; it was unclear whether allocation was concealed in two studies; and only one study clearly used ITT analysis.

Table S20—*[Section 4.4] Evidence Profile: Should Heparin vs No Heparin Be Used for Thrombosis Prophylaxis in Patients With Cancer With CVCs?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Heparin	No Heparin	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
5	Randomized trials	No serious limitations[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	31 of 671 (4.6%)	34 of 521 (6.5%)	RR, 0.85 (0.53-1.37)	10 fewer per 1,000 (from 31 fewer to 24 more)	Moderate	Critical
Symptomatic DVT												
6	Randomized trials	No serious limitations[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	17 of 664 (2.6%)	25 of 509 (4.9%)	RR, 0.54 (0.28-1.05)	23 fewer per 1,000 (from 35 fewer to 2 more)	Moderate	Critical
Major bleeding												
4	Randomized trials	No serious limitations[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	2 of 520 (0.4%)	2 of 371 (0.5%)	RR, 0.68 (0.1-4.78)	2 fewer per 1,000 (from 5 fewer to 20 more)	Moderate	Critical
Infection												
3	Randomized trials	No serious limitations[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	21 of 388 (5.4%)	17 of 238 (7.1%)	RR, 0.91 (0.49-1.68)	6 fewer per 1,000 (from 36 fewer to 49 more)	Moderate	Important
Thrombocytopenia												
3	Randomized trials	No serious limitations[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	28 of 490 (5.7%)	23 of 346 (6.6%)	RR, 0.85 (0.49-1.46)	10 fewer per 1,000 (from 34 fewer to 31 more)	Moderate	Not important
Quality of life: not reported												
0	…	…	…	…	…	None	0 of 0 (0%)	0 of 0 (0%)	…	…		Important

Bibliography: Akl EA, Vasireddi SR, Yosuico VE, Barba M, Sperati F, Cook D, Schünemann H. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. *Cochrane Database Syst Rev*. 2011;4:CD006468. See Table S4 and S12 legends for expansion of abbreviations.

[a] Allocation clearly concealed in three of the six studies. Four studies blinded patients and providers and all studies blinded outcome adjudicators. Three studies had no problem with incomplete data. None of the studies was suspected of selective reporting. Two studies clearly used ITT.

[b] Relatively small number of events.

[c] CI includes both values suggesting no effect and values suggesting either benefit or harm.

Table S21—*[Section 4.5] Evidence Profile: Should VKA vs No VKA Be Used for Thrombosis Prophylaxis in Patients With Cancer With CVCs?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	VKA	No VKA	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
2	Randomized trials	None[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	166 of 551 (30.1%)	169 of 542 (31.2%)	RR, 0.97 (0.82-1.15)	9 fewer per 1,000 (from 56 fewer to 47 more)	Moderate	Critical
Symptomatic DVT												
4	Randomized trials	None[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	37 of 621 (6%)	55 of 614 (9%)	RR, 0.63 (0.35-1.11)	33 fewer per 1,000 (from 58 fewer to 10 more)	Moderate	Critical
Major bleeding												
2	Randomized trials	None[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	7 of 551 (1.3%)	1 of 542 (0.2%)	RR, 6.93 (0.86-56.08)	11 more per 1,000 (from 0 fewer to 102 more)	Moderate Indirect evidence[e] High	Critical

Bibliography: Akl EA, Vasireddi SR, Yosuico VE Barba M, Sperati F, Cook D, Schünemann H. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. *Cochrane Database Syst Rev*. 2011;4:CD006468. VKA = vitamin K antagonist. See Table S4 and S10 legends for expansion of other abbreviations.

[a] Allocation clearly concealed in three of four studies. None of studies blinded patients, providers, or data collectors, and three studies blinded outcome adjudicators. Three studies had no problem with incomplete data. The presence of selective reporting was unclear in one study. Two studies clearly used ITT.

[b] Relatively small number of events.

[c] CI includes both values suggesting no effect and values suggesting either benefit or harm.

[d] Although data in this population are of lower quality, indirect data from many other populations that used VKA demonstrate high-quality evidence.

Table S22—*[Section 4.6] Evidence Profile: Should LMWH vs VKA Be Used for Thrombosis Prophylaxis in Patients With Cancer With CVCs?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	LMWH	VKA	Relative (95% CI)	Absolute	Quality	Importance
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	22 of 170 (12.9%)	19 of 173 (11%)	RR, 1.27 (0.55-2.96)	30 more per 1,000 (from 49 fewer to 215 more)	Low	Critical
Symptomatic DVT												
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	4 of 142 (2.8%)	3 of 138 (2.2%)	RR, 1.28 (0.25-6.5)	6 more per 1,000 (from 16 fewer to 120 more)	Low	Critical
Major bleeding												
2	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	1 of 170 (0.6%)	0 of 173 (0%)	RR, 3.1 (0.13-73.14)	0 more per 1,000 (from 0 fewer to 0 more)	Low	Critical
Thrombocytopenia												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b,c]	None	2 of 29 (6.9%)	0 of 30 (0%)	RR, 5.17 (0.26-103.21)	0 more per 1,000 (from 0 fewer to 0 more)	Low	Not important
Quality of life - not reported												
0	…	…	…	…	…	None	0 of 0 (0%)	0 of 0 (0%)	…	…		Important

Bibliography: Akl EA, Vasireddi SR, Yosuico VE D, Barba M, Sperati F, Cook D, Schünemann H. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. *Cochrane Database Syst Rev*. 2011;4:CD006468. See Table S2, S4, S10, S12, and S21 legends for expansion of other abbreviations.

[a] Allocation clearly concealed in one of the two studies. None of the studies blinded patients, providers, or data collectors, but both studies blinded outcome adjudicators. One study did not address Incomplete data reporting. None of the studies was suspected of selective reporting. One study clearly used ITT.

[b] Relatively small number of events.

[c] CI includes both values suggesting no effect and values suggesting either benefit or harm.

Table S23—*Observational Studies of Outpatients with Restricted Mobility and Nursing Home Patients*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Labarère et al[45]/2009	Two cross-sectional studies (Bosson et al[47] and Sellier et al[46]) at 50 post-acute care facilities in France	≥ 65 y; 866 LMWH and 737 non-LMWH	Prophylactic-dose LMWH vs no LMWH (32% received antiplatelet)	Proximal DVT by screening ultrasound	NA; cross-sectional study	Proximal DVT reduced by LMWH from 5.7% to 4.0% ($P = .16$); propensity analysis OR, 0.56 ($P = .03$)
Sellier et al[46]/2008	Cross-sectional study of 40 hospital-based post-acute care facilities in France	812 Patients aged ≥ 65 y	None	Proximal DVT by screening ultrasound	NA; cross-sectional study	DVT: 113 of 812 (14%); 33 (4%) had proximal DVT; independent risk factors age > 80 y (OR, 1.71), previous VTE (OR, 2.03), regional/metastatic cancer (2.71), dependent in ≥ 3 ADL (2.18), pressure ulcer (1.85)
Bosson et al[47]/2003	Cross-sectional study of 36 hospital-based post-acute care facilities in France	852 Patients aged ≥ 65 y; 52% had ≥ 2 VTE risk factors besides age	None	Proximal DVT by screening ultrasound	NA; cross-sectional study	DVT: 135 of 852 (15.8%); 50 (5.9%) had proximal DVT; prophylactic anticoagulant 56% (range 20.0%-86.9%);
Bosson et a1[13]/2006	Prospective observational cohort study	16,532 Outpatients > 40 y (median age, 71 y) with an acute medical condition reducing mobility for at least 48 h; 35% received prophylaxis	None	Symptomatic VTE	3 wk ± 7 d	VTE incidence: 197 of 16,532 (1.2%); receiving prophylaxis associated with increased incidence of VTE (confounding by indication)
Benoist et al[48]/1994 (French)	Cross-sectional study	96 Institutionalized elderly patients	None	DVT by screening ultrasound	NA	13 of 96 (13.5%) DVT; all popliteal
Gatt et al[49]/2004	Retrospective chart review	471 NH patients	None	Symptomatic VTE	Median, 2.75 y (range, 0.25-18.33)	26 Patients developed DVT symptoms; incidence similar in immobile and mobile groups (13.9 and 15.8 per 1,000 patient-years)
Kropsky et al[50]/2003	Retrospective chart review	246 NH patients taking megestrol	None	Symptomatic DVT	Not reported	10 of 246 (4.9%) DVT
Gomes[51]/2003	Retrospective cohort study using Minimum Data Set	18,661 NH patients in Kansas 1997-1998; median age, 85 y; 95% white; 74% women	None	Symptomatic VTE	Median follow-up 252 d	155 Patients developed VTE; 1.30 per 1,00 person-years

(Continued)

Table S23—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Valderrama et al[52]/2006	Prospective observational cohort study	87 NH patients	None	Asymptomatic DVT on screening ultrasound	4 mo	3 of 87 (3.4%) had DVT on initial screening at time of NH admission; 0 of 87 (0%) developed DVT over the study period
Liperoti et al[53]/2005	Retrospective cohort study using Minimum Data Set	132,018 NH residents in five US states	None	Hospitalization for VTE	6 mo	VTE hospitalization 0.91 per 100 person-years; rate was increased for users of atypical antipsychotics
Heit et al[54]/2000	Population-based nested case-control study	625 Patients (institutionalized without recent surgery) with a first VTE and 625 matched controls without a DVT	None	Risk factors for VTE		Univariate: NH confinement OR, 10.64; multivariate: "institutionalization without recent surgery" OR, 7.98
Heit et al[55]/2002	Population-based nested case-control study	625 Patients with a first VTE and 625 matched controls without a DVT	None	Attributable risk of risk factors for VTE		NH residence accounted for 13% of cases of VTE
Rodriguez-Manas et al[56]/2010	Prospective observational cohort study	Geriatric outpatient centers (n = 358) or Hospital-at-Home Units (n = 149) bedridden for at least 4 d; mean age, 82 y	LMWH (bemiparin) 2,500 or 3,500 International Units/d; no control arm	Symptomatic DVT or PE; major bleed; minor bleed, thrombocytopenia	3 mo	Three of 507 (0.6%) developed DVT; 2 (0.4%) developed major bleeding; 8 (1.6%) developed minor bleeding (excluding hematoma). Overall bleed rate 2.0%. Mild thrombocytopenia incidence, 1.4%; none < 100,000 or required discontinuation
Leibson et al[57]/2008	Nested case-control study within population-based cohort study	Olmsted County residents (n = 124,277). Used (1) MCMRP (which was a precursor to the Minimum Data Set in NHs), and (2) REP dataset	None	VTE diagnosis based on ICD-9 codes.	Followed until date of last known vital status	Yields an incidence of VTE in NH patients of 12-15 per 1,000 patient-years using MCMRP and a higher rate (36 per 1,000 patient-years) using REP. Found risk factors are unique in the NH population and relate to mobility status (ie, require assistance with transferring, need for PT, wound care) rather than the traditional risk factors (cancer, CHF).
Prieto[58]/2007 (Spanish)						0.9% VTE incidence

AD = activities of daily living; ICD-9 = International Statistical Classification of Diseases and Related Health Problems, 9th ed.; MCMRP = Minnesota Case Mix Review Program; NA, not applicable; NH = nursing home; REP = Rochester Epidemiologic Project.

Table S24—*Summary Table for Trials of Pharmacologic Prophylaxis to Prevent VTE in Air Travelers*

Study/Year	Interventions	Risk Group,† Flight Duration	Patients Analyzed (%)	Time to Screening	DVT, %, RR (95%CI)	SVT, %, RR (95%CI)	Edema, Mean (SD)‡	Comments
			LMWH vs no thromboprophylaxis					
Cesarone et al[59]/2002	No thromboprophylaxis	High, 7-8 h	No thromboprophylaxis: 83 of 100 (83)	On arrival	No thromboprophylaxis: 4 of 83 (5)	No thromboprophylaxis: 2 of 83 (2)	NR	Weight-based LMWH dosing reduces feasibility
	Enoxaparin: 1 mg/kg, 2-4 h preflight				Enoxaparin: 0 of 82	Enoxaparin: 1 of 82 (1)		
			Enoxaparin: 82 of 100 (82)		RR, 0.11 (0.00-2.06)	RR, 0.51 (0.05-5.47)		
			Aspirin vs no thromboprophylaxis					
Cesarone et al[59]/2002	No thromboprophylaxis	High, 7-8 h	No thromboprophylaxis: 83 of 100 (83)	On arrival	No thromboprophylaxis: 4 of 83 (5)	No thromboprophylaxis: 2 of 83 (2)	NR	
	Aspirin: 400 mg × 3 d, starting 12 h preflight		Aspirin: 84 of 100 (84)		Aspirin: 3 of 84 (4%)	Aspirin: 3 of 84 (4)		
					RR, 0.74 (0.17-3.21)	RR, 1.48 (0.25-8.64)		
			Pycnogenol (a bioflavonoid) vs placebo					
Belcaro et al[60]/2004	Placebo administered identically	Moderate to high, 7-12 h (mean, 8 h)	Placebo administered identically 97 of 105 (92)	< 120 min	Placebo: 1 of 97 (1.0)	Placebo: 4 of 97 (4.1)	NR	In active treatment group 1 clinical SVT seen but not classified as such—no thrombosis seen on ultrasound
	Pycnogenol 200 mg 2-3 h before flight, 200 mg 6 h later, 100 mg the next day; all with 250 mL water.		Pycnogenol 200 mg 2-3 h before flight, 200 mg 6 h later, 100 mg the next day; all with 250 mL water: 101 of 106 (95%)		Pycnogenol: 0 of 101 (0)	Pycnogenol: 0 of 101 (0)		All DVT asymptomatic. All SVT symptomatic.

NR = not reported; SVT = superficial vein thrombosis. See Table S2 and S4 legends for expansion of other abbreviations.

Table S25—*Methodologic Quality of Trials Using Pharmacologic Prophylaxis to Prevent VTE in Air Travelers*

Study/Year	Intervention	Randomization Concealed	Blinding	No Outcome (%)	Analysis	Comments
LMWH vs no thromboprophylaxis						
Cesarone et al[59]/2002	No thromboprophylaxis	Probably not (NR)	Subjects: no	No thromboprophylaxis: 17 of 100 (17)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication
						Subject recruitment process NR
	Enoxaparin 1 mg/kg, 2-4 h preflight		Outcome assessors: probably not	Enoxaparin: 18 of 100 (18)		Flight duration NR
						Method of randomization NR
						DVT screening test not validated
						Source of funding NR
Aspirin vs no thromboprophylaxis						
Cesarone et al[59]/2002	No thromboprophylaxis	Probably not (NR)	Subjects: no	No thromboprophylaxis: 17 of 100 (17)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication
						Subject recruitment process NR
	Aspirin 400 mg × 3 d, starting 12 h preflight		Outcome assessors: probably not	Aspirin: 16 of 100 (16)		Flight duration NR
						Method of randomization NR
						DVT screening test not validated
						Source of funding NR
Pycnogenol vs placebo						
Belcaro et al[60]/2004	Placebo administered identically	Unknown	Unknown for subjects or assessors	Placebo: 5 VT (1 DVT, 4 SVT [with thrombosis])	Per protocol	Outcome nonstandardized
						Preflight (within 90 min) and postflight (within 120 min) ultrasound done.
	Pycnogenol 200 mg 2-3 h before flight, 200 mg 6 h later, 100 mg the next day; all with 250 mL water.			Pycnogenol: 0 DVT, 1 SVT but not classified as such		Inconsistent reporting of completion rate of participants.
						Excluded those > 90 kg or 190 cm

See Table S2, S4, and S24 legends for expansion of abbreviations.

Table S26—*[Section 6.1.1] Evidence Profile: Should People Taking Long Flights Use Compression Stockings vs No Compression Stockings?*

Quality Assessment						Summary of Findings					
						No. of Patients			Absolute Risk		
No. of Studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Without Compression Stockings[a]	With Compression Stockings	RR (95% CI)	Control Rate	Risk Difference (95% CI)	Quality
Symptomatic DVT											
Direct evidence											
9 (RCT)	No serious limitations[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	0 of 1,323	0 of 1,314	Not estimable (no events)	0 per 1,000	0 per 1,000 (− 1.5 to 1.5)	Moderate
Indirect evidence (based on symptomless DVT as a surrogate outcome for symptomatic DVT)											
9 (RCT)	No serious limitations[b]	No serious inconsistency	Serious indirectness[d]	No serious imprecision	Undetected	Surrogate symptomless DVT: 47 of 1,323	Surrogate symptomless DVT: 3 of 1,314	RR, 0.10 (0.04-0.25)	5 per 10,000 18 per 10,000	Low risk 4.5 per 10,000 (4 to 5) High risk 16.2 per 10,000 (14 to 17.5)	Moderate
PE											
Direct evidence											
9 (RCT)	No serious limitations[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	0 of 1,323	0 of 1,314	Not estimable (no events)	0 per 1,000	0 per 1,000 (− 1.5 to 1.5)	High
Indirect evidence (based on symptomless DVT as a surrogate outcome for symptomatic DVT)											
9 (RCT)	No serious limitations[b]	No serious inconsistency	Serious indirectness[d]	No serious imprecision	Undetected	Surrogate symptomless DVT: 47 of 1,323	Surrogate symptomless DVT: 3 of 1,314	RR, 0.10 (0.04-0.25)	27 per 1 million 97 per 1 million	Low risk 24 per 1 million (20 to 26) High risk 87 per 1 million (76 to 94)	Moderate
SVT											
8 (RCT)	No serious limitations[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Undetected	12 of 901	4 of 903	RR, 0.45 (0.18-1.13)	13 per 1,000	Not significant	Moderate

(Continued)

Table S26—*Continued*

Quality Assessment						Summary of Findings					
						No. of Patients			Absolute Risk		
No. of Studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Without Compression Stockings[a]	With Compression Stockings	RR (95% CI)	Control Rate	Risk Difference (95% CI)	Quality
Edema (postflight values measured on a scale from 0, no edema, to 10, maximum edema)											
6 (RCT)	Very serious limitations[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	7- or 8-h Flight		…		Weighted mean difference: −4.72 (−4.91 to −4.52)	Low
						Mean, 6.4-6.9	Mean, 2.2-2.4			Favors stockings	
						349 Participants	348 Participants				
						12-h Flight					
						Mean, 7.9-8.9	Mean, 2.6-3.3				
						272 Participants	277 Participants				
Adverse effects[f]											
4 (RCT)	Very serious limitations[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	0 of 1,182	0 of 1,182	Not available		The tolerability of the stockings was described as very good with no complaints of side effects	Low

Bibliography: Clarke M, Hopewell S, Juszczak E, Eisinga A, Kjeldstrom M. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev.* 2006; (2):CD004002. Philbrick JT, Shumate R, Siadaty MS, et al. Air travel and venous thromboembolism: a systematic review. *J Gen Intern Med.* 2007;22:107-114. All the stockings in the nine trials included in this review were below-knee compression stockings. In four trials the compression strength was 20 to 30 mm Hg at the ankle. It was 10 to 20 mm Hg in the other four trials. Stockings come in different sizes. If a stocking is too tight around the knee it can prevent essential venous return causing the blood to pool around the knee. Compression stockings should be fitted properly. A stocking that is too tight could cut into the skin on a long flight and potentially cause ulceration and increased risk of DVT. Some stockings can be slightly thicker than normal leg covering and can be potentially restrictive with tight foot wear. It is a good idea to wear stockings around the house prior to travel to ensure a good, comfortable fitting. Stockings were put on 2 to 3 h before the flight in most of the trials. The availability and cost of stockings can vary. See Table S1, S3, S4, and S24 legends for expansion of abbreviations.

[a]Estimates for control event rates for venous thrombosis and for PE come from Philbrick et al. Definition of high risk includes previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous 2 years, large varicose veins.

[b]We did not rate down for methodological limitation, although there was inadequate concealment of allocation and blinding.

[c]The imprecision refers to absolute measures, not the relative. For the relative, it is not possible to make an estimate. This is also true for PE.

[d]There are two reasons for indirectness. One is that estimates of RR reduction come from the surrogate. The second is that there is uncertainty regarding the baseline risk.

[e]Lack of concealment and blinding constituted very serious limitations in the context of an unvalidated edema rating and description of tolerability of stockings.

[f]None of the other trials reported adverse effects, apart from four cases of SVT in varicose veins in the knee region that were compressed by the upper edge of the stocking in one trial.

Table S27—*Studies of Thromboprophylaxis to Prevent VTE in Asymptomatic Persons With Thrombophilia: Clinical Description and Results*

Study/Year, Country, Design	Interventions	No. Patients Analyzed	Length of Follow-up	Population	DVT, PE, RR (95% CI)	Deaths, Major Bleeding, RR (95%CI)	Comments
Erkan et al[61]/2002; United States; cross-sectional, retrospective, comparative cohort study	ASA, dose and duration NR	Group B: total 56; ASA: 18 of 56 (32.1%)	Group B: 6 mo prior to the patient's last hospital visit	Group B: 56 asymptomatic aPL-positive patients (medium to high titer of aCL and/or a positive LAC test but no history of vascular or pregnancy events)	Events were divided into venous or arterial events, and not specifically categorized as DVT or PE	Deaths: NR	In women only, the probability of an event increased with thrombocytopenia and the presence of either pregnancy or surgical procedures
	HCQ, dose and duration NR	HCQ: 21 of 56 (37.5%)		Age: 46.0 ± 13.8 y Sex (female): 51 of 56 (91%) Lupus-like disease: 3 of 56 (4%) (percentage is miscalculated in article; it should read 5.4%) Thrombocytopenia: 5%	"In logistic regression analysis, the probability of an event was decreased by taking ASA and/or HCQ" (compared with taking no such treatment)	Major bleeding: NR	Study excluded from Evidence Profiles for lack of appropriate data
		Group A had prior vascular event, therefore data not applicable					
Erkan et al[62]/2007; United States; RCT (APLASA study) and single-group cohort study	ASA, 81mg/d	RCT (no. randomized)	RCT: 2.30 y (SD, 0.95 y)	Persistently aPL-positive individuals (those with positive aPL but no vascular and/or pregnancy events)	RCT	Major bleeding (overt or closed-space bleeding with decrease in Hgb ≥ 2 g/dL over 24 h):	Composite outcomes only presented
	No ASA						
	Persons who declined randomization or already on ASA were followed in an observational study of ASA or no treatment	ASA: 48 Placebo: 50	Observational study: 2.46 y (SD, 0.76 y)	Observational study:	Primary outcome (incident acute thrombosis [thrombotic stroke, DVT, PE, acute MI] confirmed by imaging studies), incidence rate per 100 patient-years:	0 Groups in both studies	

(Continued)

Table S27—*Continued*

Study/Year, Country, Design	Interventions	No. Patients Analyzed	Length of Follow-up	Population	DVT, PE, RR (95% CI)	Deaths, Major Bleeding, RR (95%CI)	Comments
		Observational study ASA: 61 of 74 (82.4%)		Age, mean ± SD	ASA: 2.75		
				ASA: 47.8 ± 14.8 y	No ASA: 0		
		No ASA: 13 of 74 (17.6%)		No ASA: 46.2 ± 14.1 y	HR, 1.04 (95% CI, 0.69-1.56), $P = .83$		
				Sex (no. women),	Secondary outcome (transient ischemic attack), incidence rate per 100 patient-years:		
				ASA: 58 of 61 (95%)	ASA: 1.83		
				No ASA: 13 of 13 (100%)	No ASA: 0.86		
					HR, 1.08 (95% CI, 0.72-1.62), $P = .68$		
					Observational study primary outcome (as above):		
					ASA: 2.70		
					No ASA: 0		
					Secondary outcome: 0 both groups		
Glynn et al[63]/2007; United States; RCT (subgroup analyses of Women's Health Study)	ASA, 100 mg every 2 days for 10 y	Total No. allocated in Women's Health Study:	Median follow-up, 10.2 y (IQR, 9.7-10.6 y)	Total population: 39,876 initially healthy women age ≥ 45 y	Factor V Leiden present (unknown % had prior VTE):	NR for thrombophilia subgroup	3% of entire study population had prior VTE, but in population of interest (factor V Leiden) an uncertain % had prior VTE
	No ASA	ASA: 19,934 (5.2% had factor V Leiden = 1,037)			Rate difference per 1,000 patient-years, ASA vs placebo: −0.50 (95% CI, −2.26 to 1.26)		In patients with factor V Leiden or the prothrombin mutation, the incidence of VTE in the placebo group was 2.7 times that of women in the placebo group without either risk factor
		No ASA: 19,942 (5.1% had factor V Leiden = 1,017)					
		Total with factor V Leiden present and data for ASA effect: 1,370			HR, 0.81 (95% CI, 0.42-1.54)		

(Continued)

Table S27—*Continued*

Study/Year, Country, Design	Interventions	No. Patients Analyzed	Length of Follow-up	Population	DVT, PE, RR (95% CI)	Deaths, Major Bleeding, RR (95%CI)	Comments
Hereng et al[64]/2008; France; retrospective comparative cohort study	ASA, dose and duration NR	Total cohort 103	Mean, 64 ± 24.7 mo	All patients were asymptomatic aPL antibody-positive carriers (ACL or LAC)	Among patients with SLE, 4 of 10 not taking ASA developed a thrombosis (arterial or venous) vs 3 of 27 taking ASA (P = .03)	Deaths: NR	
	No ASA	ASA: 75 of 103 (72.8%)		Age, mean ± SD	Autoimmune thrombocytopenia: 4 of 6 patients not taking aspirin suffered a thrombotic event vs 1 of 10 taking aspirin (P = .01)	"Severe bleeding event" (not defined):	
		No ASA 28 of 103 (27.2%)		ASA: 40.1 ± 16.7 y		ASA: 0 of 75 (0%)	
				No ASA: 44.7 ± 17.4 y		No ASA: 0 of 28 (0%)	
				Sex (no. women):			
				ASA: 67 of 75 (89.3%)			
				No ASA: 24 of 28 (85.7%)			
				Associated diseases: SLE (n = 37), autoimmune thrombocytopenia (n = 16), RA (n = 8)			
Tektonidou et al[65]/2009; Greece; prospective comparative cohort study	ASA, 80-100 mg/d	All patients with SLE with positive aPL without previous thrombosis or pregnancy morbidity: n = 144	Median duration of follow up, aPL-positive patients: 104 mo (IQR, 61-150 mo)	Patients with SLE with positive aPL but without previous thrombosis or pregnancy morbidity	Overall acute thrombosis incidence rate (events per 100 patient-years):	No patient experienced major bleeding in either SLE group	Variables associated with thrombotic events in aPL-positive patients: male sex, LAC, constantly positive aCL
			aPL-negative patients: 112 mo (IQR, 62-156 mo)	Thrombotic events, No. (%)	aPL-positive: 2.09		
					aPL-negative: 0.79		
	HCQ, dose NR	Age- and sex-matched patients with SLE with negative aPL: n = 144		aPL-positive: 29 of 144 (20%)			
				aPL-negative: 11 of 144 (7.6%)			
		11 of 87 patients took ASA;		(7 arterial, 4 venous)		Death: NR	
		19 of 101 took HCQ (could use both)		P = .003			

(Continued)

Table S27—*Continued*

Study/Year, Country, Design	Interventions	No. Patients Analyzed	Length of Follow-up	Population	DVT, PE, RR (95% CI)	Deaths, Major Bleeding, RR (95%CI)	Comments
					Unadjusted RR in aPL-positive patients for treatment: ASA vs no ASA for thrombosis: HR, 0.43; 95% CI, 0.20-0.91; $P = .027$		
					HCQ: HR, 0.67 (95% CI, 0.31-1.45), $P = .30$		
					Adjusted analyses: HR per 1 mo in aPL-positive patients for risk of thrombotic events:		
					ASA vs no ASA: HR, 0.98 (95% CI, 0.96-0.99), $P = .05$		
					HCQ vs none: HR, 0.99 (95% CI, 0.98 to 1.00), $P = .05$		
					Combination therapy results NR		

aCL = anticardiolipin; aPL = antiphospholipid antibodies; HCQ = hydroxychloroquine; LAC = lupus anticoagulant; SLE = systemic lupus erythematosus. See Table S1, S3, S4, S7, S17, and S24 legends for expansion of abbreviations.

Table S28—*RCTs of Thromboprophylaxis to Prevent VTE in Asymptomatic Persons With Thrombophilia: Methodologic Quality*

Study/Year	Concealment of Allocation	Blinding of Patients	Blinding of Health-care Providers	Blinding of Data Collectors	Blinding of Outcome Adjudicators	Blinding of Data Analysts	Stopped Early For Benefit	ITT Comments
Erkan et al[62]/2007	DY	DY	DY	DY	PY	PY	DY	DY
	Centralized allocation with computer-generated randomization table	"Investigators, coordinators, participants were blinded to the treatment assignments"					Patient recruitment terminated early as lower-than-expected event rates in both groups; larger sample size unfeasible	
Glynn et al[63]/2007	DY	DY	DY	DY	DY	DY	No	DY
Subgroup analysis of RCT (Women's Health study)								Subgroup analyses were prespecified. In population of interest (factor V Leiden) an uncertain % had prior VTE; in overall population 2.9% had prior VTE, but in patients with factor V Leiden or the prothrombin mutation the incidence of VTE in the placebo group was 2.7 times that of women in the placebo group without either risk factor

DY = definitely yes; PY = probably yes. See Table S3 and S10 legends for expansion of other abbreviations.

Table S29—*Observational Studies of Thromboprophylaxis to Prevent VTE in Asymptomatic Persons With Thrombophilia: Methodologic Quality*

Study/Year	Intervention/ Comparator	Study Design	Intervention/Control Setting Similar	Intervention/Control Time Frame Similar	Adjustment	Effectively Blinded Assessment of Outcome	Loss to Follow-up
Erkan et al[62]/2007	ASA, 81 mg/d No ASA	Prospective comparative cohort study (RCT quality is assessed in separate table)	DY	DY Follow-up intervals similar, contemporaneous data collection	NR	PY	ASA: 2 of 61 (3.3%); 6 withdrawals No ASA: 0 of 13 (0%); 2 withdrawals
Erkan et al[61]/2002	Both ASA and HCQ examined (study excluded from Evidence Profile) ASA (dose and duration NR) vs no treatment HCQ (dose and duration NR) vs no treatment	Cross-sectional, retrospective, comparative study	PY	PY	NR Group A had had an event, Group B was asymptomatic; significant differences between the two groups	DN	NA (retrospective)
Hereng et al[64]/2008	ASA: dose and duration NR No ASA	Retrospective comparative cohort study	PY (10 patients were not followed in same department)	DY	NR Groups differed on % aCL, IgG, and IgM ($P < .05$), thus differ in thrombosis risk	DN	3 of 108 (27.8%) other patients received long-term anticoagulation
Tektonidou et al[65]/2009	Both ASA and HCQ examined ASA (80-100 mg/d) vs no treatment HCQ (dose NR) vs no treatment	Prospective comparative cohort study	DY Recruited from same clinic	DY	Sex, LAC, age, smoking, comorbid conditions	PN	Cohort was followed to date of last visit or to event

DN = definitely no; PN = probably no. See Table S7, S24, S27, and S28 legends for expansion of abbreviations.

Table S30—*[Section 7.1]—Evidence Profile: Should ASA vs No Treatment Be Used for Prevention of VTE in Persons With Asymptomatic Thrombophilia?*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	ASA	No Treatment	Relative (95% CI)	Absolute	Quality	Importance
VTE (nonfatal) (follow-up, 2.3-10.1 y)												
2[a]	Randomized trials[b]	No serious limitations[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2 of 48 (4.2%)[e]	1 of 50 (2%)	RR, 2.08 (0.20-22.23)	22 more per 1,000 (from 16 fewer to 425 more)	Low	Important
Mortality (follow-up mean, 2.3 y)[f]												
1[g]	Randomized trials	Serious[c]	No serious inconsistency[h]	No serious indirectness	Serious[d]	None	1 of 50 (2%)[i,j]	1 of 48 (2.1%)[k]	RR, 1.04 (0.07-16.19)[l,m]	1 more per 1,000 (from 19 fewer to 316 more)	Low	Critical
Major bleed (nonfatal) (follow-up, 2.3-8 y)												
3[g,n]	Observational studies[n]	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	0 of 147 (0%)[o]	0 of 60 (0%)	Not pooled[p]	Not pooled	Very low	Important

Bibliography: Glynn RJ, Ridker PM, Goldhaber SZ, Buring JE. Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial.[Summary for patients in *Ann Intern Med.* 2007;147(8):I34; PMID: 17938386]. *Ann Intern Med.* 2007;147(8):525-533. Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum.* 2007;56(7):2382-2391. Hereng T, Lambert M, Hachulla E, et al. Influence of aspirin on the clinical outcomes of 103 anti-phospholipid antibodies-positive patients. *Lupus.* 2008;17(1):11-15. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum.* 2009;61(1):29-36. See Table S1, S3, S4, S7, and S11 legends for expansion of abbreviations.

[a] Erkan et al and Glynn et al are RCTs; in addition, Hereng et al, Erkan et al, and Tektonidou et al provided observational data.

[b] Erkan et al and Glynn et al.

[c] Erkan et al terminated early as event rates were lower than expected and larger sample size was infeasible.

[d] Number of events was very small.

[e] Event rates are from Erkan et al (RCT) (n = 98), as second RCT (Glynn et al) did not report event rates. In Erkan et al, HR of composite outcome (arterial or venous thrombosis, including stroke, PE, DVT, acute MI), 1.04 (95% CI, 0.69-1.56), $P = .83$. Number of venous events: intervention 2 of 48, placebo 0 of 50. Glynn et al (RCT, n = 1,370), HR for VTE, 0.81 (95% CI, 0.42-1.54). In addition, observational studies reported composite outcomes including both arterial and venous events (Erkan et al, Hereng et al, and Tektonidou et al).

[f] In addition to the RCT, one observational study had follow-up of 2.5 y (SD, 0.8 y).

[g] Erkan et al encompasses both an RCT and an observational study.

[h] Inconsistency not assessed as is one study, although Erkan et al encompasses both a relevant RCT and an observational component.

[i] Intervention was 81 mg od.

[j] Cause of death was not reported.

[k] Comparison group received no ASA.

[l] RR calculated from event rates (unadjusted).

[m] In addition, in the observational study (Erkan et al) the mortality rate was 0% in both groups.

[n] Erkan et al, Hereng et al, Tektonidou et al. In addition, Erkan et al (RCT) reported 0 major bleeding events both groups.

[o] Erkan et al also included an RCT (n = 94) with 0 major nonfatal bleeding events in both the ASA and no ASA groups.

[p] RR not estimable (rate of 0 both groups).

Table S31—*Studies Examining the Effect of Exposure to Statins on DVT, PE, and death: Clinical Description and Results: RCT and Cohort Studies*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
Grady et al[66], 2000; United States; Prospective, comparative cohort study from HERS trial	Statin therapy	2,763 Women randomized in HERS trial (1,380 randomized to receive estrogen; 1,383 to placebo)	Postmenopausal women < 80 y, with CHD but no previous VTE and no hysterectomy	HERS trial: mean follow-up 4.1 y (range 3.6-5.3 y)	Clinical events according to statin use during the HERS trial:	Interaction between hormone replacement therapy and statin use for 1-y events: $P = .57$
	No statin therapy			Mean duration of follow-up: 3.3 y	Baseline use	
			Mean age ± SD, y			
				Duration of follow-up for women who used statins for ≥ 3 y (mean ± SD): 5.7 ± 2.4 y		
		Statin therapy: 1,004	Statin therapy: 66.9 ± 6.18			
		No statin therapy: 1,467	No statin therapy: 66.5 ± 7.04		VTEs:	
			Sex: 100% women		No statin use: 32 of 1,467 (5.5[a])	
				Duration of follow-up for women who used statins for < 3 y (mean ± SD): 5.7 ± 2.4 y		
			Baseline statin users tended to be white, better educated, healthier, with few comorbid conditions and more likely to take ASA		Statin use: 9 of 1,004 (2.2[a])	

(Continued)

Table S31—*Continued*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
					Adjusted HR: 0.44 (95% CI, 0.21-0.94), $P = .033$	
					All-cause mortality	
					No statin use: 159 of 1,467 (26.8[a])	
					Statin use: 75 of 1,004 (18.4[a])	
					Adjusted HR: 0.74 (95% CI, 0.56-0.99), $P = .040$	
					Any statin use	
					VTEs:	
					No statin use: 28 of 1,467 (6.1[a])	
					Statin use: 13 of 1,270 (2.5[a])	
					Adjusted HR: 0.45 (95% CI, 0.23-0.88), $P = .020$	
					Mortality	
					No statin use: 134 of 1,467 (28.4[a])	
					Statin use: 100 of 1,270 (18.9[a])	
					Adjusted HR: 0.67 (95% CI, 0.51-0.87), $P = .003$	
					Used statins > 3 y	
					All-cause mortality: HR, 0.70 (95% CI 0.52-0.93), $P = .01$	
					VTEs: HR, 0.40 (95% CI, 0.18-0.91), $P = .03$	

(Continued)

Table S31—*Continued*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
Ray et al,[67] 2001; Canada; Retrospective cohort study	Primary cohort: Statins Thyroid replacement therapy Non-statin lipid-lowering agents Secondary cohort (women only): as for primary cohort, plus estrogens	Primary cohort: 125,862 adults; 190,601 person-years of drug use Secondary cohort: 89,508 women; 124,568 person-years of drug use	Ontario residents aged ≥ 65 y enrolled in the Ontario Health Insurance Plan Mean age (primary cohort), 72.9 y Mean age (secondary cohort), 73.5 y Since estrogen use in the secondary cohort had to be mutually exclusive, these participants may have differed slightly from women in the primary cohort	The average duration of observation 1.4 y for both statins and thyroid replacement therapy (primary cohort)	No. of cases of DVT/1,000 patient-years (adjusted HR [95% CI]) Primary cohort Men and women Receiving thyroid replacement therapy: 10.9 (HR, 1.0 [referent]) Receiving non-statin lipid-lowering agents: 9.3 (HR, 0.97 [0.79-1.18]) Receiving statin therapy: 7.4 (HR, 0.78 [0.68-0.87]) Men	

(Continued)

Table S31—*Continued*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
					Receiving statin therapy: 6.7 (HR, 0.97 [0.78-1.22])	
					Women	
					Receiving statin therapy: 8.1 (HR, 0.72 [0.63-0.82])	
					Secondary cohort:	
					Thyroid replacement therapy: 11.9 (HR, 1.0 [referent])	
					Statin therapy: 7.6 (HR, 0.68 [0.59-0.79])	
Smeeth et al[68]/2009; United Kingdom; observational study, population based	Various statins (first prescription) compared with non-statin users (no record of statin use)	Total N, 729,529 Statin users: 129,288 Non-statin users: 600,241	THIN database: age 40-80 y between January 1995 and December 2006 5.5 million patients derived from 303 general practices	Median follow-up after index date (date of first use of statin): 4.4 y	VTE risk in exposed 1.1%, unexposed 1.0%; HR adjusted for age and sex, 1.18 (95% CI, 1.06-1.31); HR fully adjusted. 1.02 (0.88-1.18)	
Glynn et al[69]/2009; United States Ridker et al[70]/2008; United States Ridker et al[71]/2007; United States; JUPITER trial; RCT	Rosuvastatin (20 mg/d) Placebo	Total: 17,802 Rosuvastatin: 8,901 Placebo: 8,901	Apparently healthy subjects with LDL cholesterol (< 130 mg/dL) and elevated high-sensitivity C-reactive protein (± 2.0mg/L), men ≥ 50 y and women ≥ 60 y Among all 17,802 JUPITER patients:	Median follow-up: 1.9 y (maximum 5.0 y)	Primary efficacy analysis[b] PE (No. patients, No. events per 100 person-years) Rosuvastatin: 17, 0.09 Placebo: 22, 0.12 HR (95% CI): 0.77 (0.41-1.45), $P = .42$	DVT diagnosed with ultrasound or venogram; PE diagnosed with angiogram, CT scan, or V̇/Q̇ scan

(Continued)

Table S31—*Continued*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
			32.0% were ≥ 70 y of age		DVT (No. patients, No. events per 100 person-years)	
			38.2% were women			
			Age, median			
			Rosuvastatin: 66.0 y		Rosuvastatin: 17, 0.09	Consistent effects in all subgroups examined
			Placebo: 66.0 y			
			Sex (% female)		Placebo: 38, 0.20	
			Rosuvastatin: 3,426 of 8,901 (38.5%)			
			Placebo: 3,375 of 8,901 (37.9%)		HR (95% CI): 0.45 (0.25-0.79), $P = .004$	Bleeding (not defined): rosuvastatin: 258 of 8,901 (2.9%)
			High-sensitivity C-reactive protein ≥ 5 mg/L (%) Rosuvastatin: 40.6%			
			Placebo: 41.9%			
			In both rosuvastatin and placebo groups, 37.6% had a BMI ≥ 30			
						Placebo: 275 of 8,901 (3.1%), $P = .45$
					Safety analysis[c]	
					PE (No. patients, No. events per 100 person-years)	
					Rosuvastatin: 17, 0.09	
					Placebo: 24, 0.12	

(Continued)

Table S31—*Continued*

Study/Year; Trial Name; Country; Study Design	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up	Results	Comments
					HR (95% CI): 0.71 (0.38-1.32), $P = .27$	ICH (number): rosuvastatin: 6 (0.1%)
					DVT (No. patients, No. events per 100 person-years)	
					Rosuvastatin: 18, 0.09	
					Placebo: 40, 0.21	Placebo: 9 (0.1%), $P = .44$
					HR (95% CI): 0.45 (0.26-0.78), $P = .003$	GI bleeding event: NR specifically; no significant difference between groups in GI "systems"
					Mortality in VTE: Among the 94 participants (34 in rosuvastatin group and 60 in placebo group) in whom VTE developed, 21 died by March 30, 2008 (14 in the placebo group and 7 in the rosuvastatin group) (HR, 0.88; 95% CI, 0.35-2.18; $P = .78$)	
					All-cause mortality: 1.00 and 1.25 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR, 0.80; 95% CI, 0.67-0.97; $P = .02$)	

CHD = coronary heart disease; ICH = intracranial hemorrhage; HERS = Heart and Estrogen/Progestin Replacement Study; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein; THIN = The Health Improvement Network. See Table S1 and S3 legends for expansion of abbreviations.

[a] Events per 1,000 patient-year follow-up.

[b] Performed on the basis of 94 cases identified before March 20, 2008, when trial stopped early for efficacy.

[c] Performed on the basis of 99 cases that were identified before the study was unblended.

Table S32—*Studies Examining the Effect of Exposure to Statins on DVT, PE, and Death: Clinical Description and Results: Case-Control Studies*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Brophy et al[72]/2009; United States	Statin use vs no statin use	Cases: 60 Controls: 41	Age:	NA: current statin use assessed by self-report	Statin use and cases of vascular access thrombosis:	
	Cases: patients who (1) experienced two or more episodes of vascular access thrombosis in 12 mo diagnosed by ultrasound, fistulogram, or physical examination; and (2) required two or more new dialysis access placements not related to infection in 2 y; or (3) patients who could not maintain a patent AVG or AVF within 2 mo that necessitated placement of a permanent catheter or the permanent conversion to peritoneal dialysis.		I: 53.8 y (SD, 14.2 y)		Cases: 18 of 60 (31%)	
					Controls: 8 of 41 (20.5%)	
					P = .35	
			C: 54.8 y (SD, 10.2 y)		Multivariable logistic regression for vascular access thrombosis: OR, 5.12 (95% CI, 1.25-20.90); *P* = .02	
			P = .69			
			Sex, female:			
			I: 27 (45%)			
			C: 16 (39%)			
			P = .55			
			Race, black:			
			I: 55 (92%)			
	Controls: patients who had not experienced vascular access thrombosis in at least 3 y		C: 39 (95%)			
			P = .49			
			All patients had stage 5 chronic kidney disease and received maintenance hemodialysis for > 3 y			

(Continued)

Table S32—*Continued*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Doggen et al[73]/2004; United States	All cases had a first venous thrombosis between January 1, 1995 and December 31, 2000 and were taking: Cases: I1: No lipid-lowering medication I2: Statin users (simvastatin, low dose and high dose; and pravastatin) I3: Users of non-statin lipid-lowering medications, including bile-acid sequestrants, fibrates, and niacins Controls: frequency matched on age, calendar year of identification, and treated hypertension status to distributions of MI cases	Cases: 465 (DVT in the leg, 348; PE, 42; both, 75) Controls: 1,962	Age: 30-89 y Sex: 100% women Inclusion criteria: all patients were postmenopausal	NR; duration of use calculated from pharmacy records	Venous thrombosis (DVT and/or PE) (first OR adjusted for matching factors, second OR also adjusted for vascular disease history): Any statin use vs no use: OR, 0.84 (95% CI, 0.51-1.37) OR, 0.64 (95% CI, 0.39 to 1.07) Use of simvastatin: OR, 0.69 (95% CI, 0.40-1.20) OR, 0.51 (95% CI, 0.29 -0.91) Data also presented on low and high dose simvastatin Use of pravastatin: OR, 2.30 (95% CI, 0.81-6.49) OR, 1.85 (95% CI, 0.65-5.26) Use of other lipid-lowering agents: OR, 1.68 (95% CI, 0.75-3.79) OR, 1.43 (95% CI, 0.62-3.25)	Current use defined as: the receipt of at least one lipid-lowering prescription prior to the index date with enough medications to last until the index date, assuming 80% compliance

(Continued)

Table S32—*Continued*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Lacut et al[74]/2004; France; EDITH	Cases: patients with documented symptomatic DVT of the lower limbs (either distal or proximal confirmed by duplex ultrasonography) or/and an objectively documented PE, not related to a major acquired risk factor for VTE	Cases: 377 (DVT, 252; PE, 46; both, 79)	Age:	Controls followed for up to 3 mo for VTE	Statin use, cases of VTE: I: 20 of 377 C: 44 of 377 OR, 0.42 (95% CI, 0.23-0.76); $P = .002$	Populations in Lacut 2004[74] and 2008[75] overlap. The 2008 publication included longer recruitment period but only included cases without major risk factors for VTE, whereas Lacut 2004 included 69 of 377 patients in each group with major acquired risk factors for VTE
	Controls: hospitalized patients matched for age (± 2 y), sex, geographical origin, and major acquired risk factors of VTE, and no prior VTE	Controls: 377	Cases: 68.0 y (SD, 16.4 y) C: 68.1 y (SD, 16.2 y) $P = .90$ Sex, female: Cases: 211 (55.9%) C: 211 (55.9%) Inclusion criteria: Patients > 18 y of age hospitalized between May 2000 and May 2002	Current statin use was considered (within prior 3 mo)	Statins included pravastatin, simvastatin, atorvastatin; results not stratified by specific statin	Stratified analyses of various levels of ASA use, CAD, secondary vs idiopathic VTE, age, sex did not significantly interact with odds of VTE

(Continued)

Table S32—*Continued*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Lacut et al[75]/2008; France; EDITH	Cases: patients with an objectively confirmed symptomatic VTE and no major acquired risk factor for VTE	Cases: 677 (DVT, 303; PE, 121; both, 256)	Age:	Current statin use (taken within 1 wk)	Current statin use:	
	Controls: patients matched by age (± 5 y) and sex and without a previous episode of objectively documented VTE or lifelong anticoagulant therapy	Controls: 677	I: 67.9 y (SD, 17.0 y)		Cases: 55 (8.1%)	
			C: 68.0 y (SD, 17.0 y)		C: 91 (13.4%)	
			Sex, female:		OR VTE in statin vs non user, 0.53 (95% CI, 0.37-0.78)	
			I: 56.7%		Adjusted OR, 0.60 (0.39-0.93)	
			C: 56.7%		Adjusted for atherothrombosis, aspirin use, suspected as the main confounding factors, and chronic pulmonary disease, BMI, and family history of VTE	
			BMI:			
			I: 26.1 (SD, 4.7)			
			C: 24.7 (SD, 5.6)			
			$P < .0001$			
			Inclusion criteria, cases and controls: patients > 18 y of age hospitalized between May 2000 and December 2004, without major acquired risk factor of VTE (no surgery or plaster cast immobilization in the past 3 mo, pregnancy or delivery in the past 3 mo, or active cancer)			

(Continued)

Table S32—*Continued*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Ramcharan et al[76]/2009; Netherlands	Statin use, current (used medication at time of the VTE or when questionnaire filled out [controls])	Entire study: 4,538 cases of VTE, 154 used statins 5,914 control subjects, matched on age and sex, 354 used statins	Age: 18-70 y, median 49.6 y (25.7-67.8 y) for cases; 48.3 y (25.7-66.8 y) for controls (54.2% female for cases, 53.8% for controls) Cases of first episode DVT and/or PE (probable or definite) were obtained from a large population-based study (MEGA study) Controls were partners of patients or were recruited via random-digit dialing Cases had higher BMI and more often had atherosclerotic disease and malignancy, diabetes, or surgery, as compared with control subjects (Table 1, statistics not reported)	12 mo prior to index case/date	"Venous thrombosis": statin current use vs no statin use: OR, 0.55 (95% CI, 0.46-0.67) (unadjusted) OR adjusted for age, sex, BMI, atherosclerotic disease, and the other medications, 0.45 (95% CI, 0.36-0.56) DVT pravastatin vs simvastatin adjusted OR, 0.59 (95% CI, 0.31-1.11) PE: adjusted OR, 0.56 (95% CI 0.43-0.75) DVT: adjusted OR, 0.31 (95% CI 0.23-0.42)	"Venous thrombosis" was the reported outcome and appears to include DVT and/or PE

(Continued)

Table S32—*Continued*

Study/Year; Trial Name; Country	Intervention and Comparator	Sample Size	Population Characteristics	Length of Follow-up, Mean	Results	Comments
Sorensen et al[77]/2009; Denmark	Statin use in last 1 y	5,824 Patients with VTE and 58,240 controls matched on age, sex, county	Age > 71 y: 47.8%; range, 18-89 y	NA	Prevalence of statin use in VTE patients 4%, controls 4%	
	Current use: ≤ 90 d		Female: 54.7%		Current statin use:	
	Former use: 91-365 d	3,366 Were unprovoked (no risk factors): 2,310 with DVT and 1,056 with PE			VTE: OR, 0.74 (95% CI, 0.63-0.85	
					Unprovoked VTE: OR, 0.79 (95% CI, 0.65-0.96)	
					DVT: OR, 0.81 (95% CI, 0.68-0.97)	
					PE: OR, 0.61 (95% CI, 0.48-0.78)	
					Former statin use:	
					VTE: OR, 0.70 (0.53-0.92)	
					Unprovoked VTE: OR, 0.97 (95% CI, 0.69-1.36)	
					All OR are adjusted for multiple potential confounders	
Yang et al[78]/2002; United Kingdom	Current/recent (≤ 90 d) and past > 90 d statin use	Total N = 84,093 (cohort study)	General Practice Research Database was used.	Cohort study: 393,756 person-years	Cohort study	
	Reference group was the non-hyperlipidemic non-statin users	Case-control study	First idiopathic VTE, confirmed or probable			
		Cases: 72				
		Controls: 432	Controls: 6 matched controls: age, sex, calendar time, time in database	Case-control study: NR (time of potential exposure)	VTE and current statin use: Adjusted rate ratio, 0.8 (95% CI, 0.3-2.7)	
					Adjusted RR with past statin use, 2.4 (0.6-10)	
					Case-control study	
					VTE, current/recent statin use: OR adjusted for smoking, BMI, and estrogen use, 1.1 (95% CI, 0.3-4.3)	
					VTE: past statin use: OR adjusted for smoking, BMI, and estrogen use, 3.7 (95% CI, 0.6-24)	

AVF = arteriovenous fistula; C = control; CAD = coronary artery disease; EDITH = Etudes des Déterminants et Interactions de la Thrombose Veineuse; I = intervention; MEGA = Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis. See Table S1, S3, and S7 legends for expansion of other abbreviations.

Table S33—*[Section 8.1] Effect of Statins on Risk of VTE*

Quality Assessment							Summary of Findings					
							No. of Patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Statins	No Statin Use	Relative (95% CI)	Absolute	Quality	Importance
DVT (follow-up median, 1.9 y; ultrasound or venogram)												
1	Randomized trials[a]	No serious limitations	No serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	None	17 of 8,901 (0.2%)	38 of 8,901 (0.4%)	HR, 0.45 (0.25-0.79)	2 fewer per 1,000 (from 1 fewer to 3 fewer)	High	Yes, clinically diagnosed DVT
PE (follow-up median, 1.9 y; angiogram, V̇/Q̇ scan, or CT scan)												
1	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	17 of 8,901 (0.2%)	22 of 8,901 (0.2%)	HR, 0.77 (0.41-1.45)	0 fewer per 100 (from 0 fewer to 0 more)	High	Yes, clinically diagnosed PE

See Table S1 and S3 legends for expansion of abbreviations.

[a] Body of evidence consists of one RCT. Six case-control studies and three observational studies are described in the text.

[b] Inconsistency is not applicable as there is only one study. Observational data were, however, consistent with the trial data.

[c] The single RCT (JUPITER, Glynn et al[69]) was a large international study including healthy subjects without diabetes, cardiovascular disease, or kidney disease, with LDL cholesterol < 130 mg/dL and C-reactive protein > 2 mg/L. Results may then be applicable only to similar persons.

[d] The number of events was low for VTE (DVT + PE): intervention 34, control 60, which is much less than the optimal information size. However, the total sample size was large (8,901 each group), so imprecision not likely.

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