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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

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.** ***CHEST 2012; 141(2)(Suppl):e195S–e226S***

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	Anticipated Absolute Effects: 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 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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