

Venous Thromboembolism Prophylaxis in Hospitalized Patients: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Roger Chou, MD; Linda L. Humphrey, MD, MPH; Melissa Starkey, PhD; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on prophylaxis of venous thromboembolism for hospitalized nonsurgical patients (medical patients and patients with acute stroke).

Methods: This guideline is based on published literature on the topic from 1950 through April 2011 that was identified by using MEDLINE, the Cochrane Library, and reference lists of pertinent randomized trials and systematic reviews to identify additional reports. Searches were limited to randomized trials and English-language publications. The primary outcome for this guideline was total mortality up to 120 days after randomization. Secondary outcomes included symptomatic deep venous thrombosis; all pulmonary embolisms; fatal pulmonary embolism; all bleeding events; major bleeding events; and, for mechanical prophylaxis, effects on skin. This guideline grades the evidence and recommendations by using the ACP's clinical practice guidelines grading system.

Recommendation 1: ACP recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) pa-

tients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).

Recommendation 2: ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).

Recommendation 3: ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).

Policy Implication: ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal venous thromboembolism prophylaxis regardless of risk.

Ann Intern Med. 2011;155:625-632.
For author affiliations, see end of text.

www.annals.org

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep venous thrombosis (DVT), is a common clinical problem and is associated with substantial morbidity and mortality (1). Most hospitalized medical patients have at least 1 risk factor for VTE, and this risk persists for several weeks after discharge (1). Twenty-six percent of patients with undiagnosed and untreated PE will have a subsequent fatal embolic event, whereas another 26% will have a nonfatal recurrent embolic event (2). Studies show that between 5% and 10% of all in-hospital deaths are a direct result of PE (3–5). The incidence of PE in the United States is estimated to be 1 case per 1000 persons per year, and PE accounts for 200 000 to 300 000 hospitalizations per year (6, 7).

The purpose of this guideline is to present clinical recommendations on prophylaxis of VTE in adult hospitalized medical patients and patients with acute stroke, based on the available evidence on the benefits and harms of prophylaxis of VTE in these patient populations. The target audience for this guideline is all clinicians, and the tar-

get patient population is all hospitalized nonsurgical patients who are at risk for VTE.

METHODS

The guideline is based on a systematic evidence review that addressed the following questions:

Key question 1: What are the benefits and harms of subcutaneous low-dose heparin products for VTE prophylaxis in hospitalized medical patients?

See also:

Print

Editorial comment. 638
Related article. 602
Summary for Patients. I-38

Web-Only

CME quiz (preview on page I-22)
Conversion of graphics into slides

* This paper, written by Amir Qaseem, MD, PhD, MHA; Roger Chou, MD; Linda L. Humphrey, MD, MPH; Melissa Starkey, PhD; and Paul Shekelle, MD, PhD, was developed for the Clinical Guidelines Committee of the American College of Physicians: Paul Shekelle, MD, PhD (*Chair*); Roger Chou, MD; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Nick Fitterman, MD; Mary Ann Forciea, MD; Robert H. Hopkins Jr., MD; Linda L. Humphrey, MD, MPH; Tanveer P. Mir, MD; Holger J. Schünemann, MD, PhD; Donna E. Sweet, MD; and David S. Weinberg, MD, MSc. Approved by the ACP Board of Regents on 30 July 2011.

Table. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Key question 2: What is the comparative effectiveness of different low-dose heparin products (low-molecular-weight heparin [LMWH], unfractionated heparin [UFH]) for VTE prophylaxis?

Key question 3: What is the effectiveness and comparative effectiveness of mechanical devices for VTE prophylaxis?

Key question 4: Do results vary by general medical patient populations: general medical inpatients and patients with acute stroke?

The systematic evidence review was conducted by the Minnesota Evidence-based Practice Center (8). The literature search included studies identified by using MEDLINE and the Cochrane Library for clinical trials of VTE prophylaxis. The authors reviewed titles and abstracts of identified references and used reference lists of pertinent randomized trials and systematic reviews to identify additional reports. The studies selected included English-language, randomized trials published between 1950 and April 2011. Included trials evaluated treatments that are commonly recommended and used to prevent VTE, including subcutaneous low-dose (<20 000 U/d) UFH or similar prophylactic doses of LMWH or related agents (such as fondaparinux) and graduated compression stockings or other mechanical measures (such as intermittent pneumatic compression). The primary outcome of interest was total mortality up to 120 days after randomization. Secondary outcomes included symptomatic DVT; all PEs; fatal PE; all bleeding events; and major bleeding events (variably defined by trials, but typically defined as a decrease in hemoglobin level >20 g/L, transfusion of ≥ 2 units of blood, or life-threatening bleeding at a critical site); and, for mechanical prophylaxis, effects on skin. Details regarding the review methods can be found in the accompanying evidence review (8). To guide our recommendations, we prioritized outcomes on the basis of clinical importance, starting with total mortality. In the absence of statistically significant effects on total mortality, we then weighted effects on all PEs versus effects on major bleeding events, followed by

symptomatic DVT, all bleeding (including minor bleeding) events, and effects on skin.

This guideline rates the evidence and recommendations by using the guideline grading system of the American College of Physicians (ACP), which is based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (Table). Details of the ACP guideline development process can be found in the methods article (9).

BENEFITS AND HARMS OF HEPARIN PROPHYLAXIS VERSUS NO HEPARIN PROPHYLAXIS

Medical Patients

Ten trials (10–19) ($n = 20\,717$) evaluated medical patients without stroke. The results showed that compared with no heparin prophylaxis, heparin prophylaxis was not associated with a statistically significant reduced risk for mortality (risk ratio [RR], 0.94 [95% CI, 0.84 to 1.04]; $I^2 = 0\%$; absolute reduction, 4 events per 1000 persons treated [CI, –11 to 3 events]) (moderate-quality evidence). However, heparin prophylaxis was associated with a reduced risk for PE (RR, 0.69 [CI, 0.52 to 0.90]; $I^2 = 0\%$; absolute reduction, 4 events per 1000 persons treated [CI, –6 to –1 event]) (moderate-quality evidence) but an increased risk for all bleeding events (RR, 1.34 [CI, 1.08 to 1.66]; absolute increase, 9 events per 1000 persons treated [CI, 2 to 18 events]) (moderate-quality evidence). Although the risk for major bleeding events increased, the difference did not reach statistical significance (RR, 1.49 [CI, 0.91 to 2.43]; $I^2 = 16\%$; absolute increase, 1 event per 1000 persons treated [CI, 0 to 4 events]) (low-quality evidence). Also, heparin prophylaxis resulted in an absolute reduction of 2 fewer symptomatic DVTs per 1000 patients treated (CI, –6 to 4 events), although the difference was not statistically significant (RR, 0.78 [CI, 0.45 to 1.35]) (low-quality evidence).

Acute Stroke

Evidence from 8 trials (20–27) ($n = 15\,405$) of patients with acute stroke showed that compared with no heparin prophylaxis, heparin prophylaxis was not associated with a statistically significant reduction in risk for mortality (RR, 0.91 [CI, 0.70 to 1.18]; $I^2 = 32\%$; absolute reduction, 9 events per 1000 persons treated [CI, –29 to 18 events]) (low-quality evidence), PE (RR, 0.72 [CI, 0.50 to 1.04]; $I^2 = 20\%$; absolute reduction, 3 events per 1000 persons treated [CI, –5 to 0 events]) (low-quality evidence), or symptomatic DVT (RR, 0.14 [CI, 0.00 to 7.09]; absolute reduction, 9 events per 1000 persons treated [CI, –10 to 57 events]) (low-quality evidence). Heparin prophylaxis was associated with an increased risk for major bleeding events (RR, 1.66 [CI, 1.20 to 2.28]; $I^2 = 0\%$; absolute increase, 6 events per 1000 persons treated [CI, 2 to 12 events]) (moderate-quality evidence). The pooled trials were heterogeneous in their patient samples and treatment. The strongest evidence on the benefits

and harms of VTE prophylaxis came from a single large randomized, controlled trial of patients with acute ischemic stroke ($n = 14\,578$ [excluding patients randomly assigned to high-dose heparin]) (21). It found no statistically significant difference between low-dose heparin and no heparin in 14-day all-cause mortality (8.7% vs. 9.3%; RR, 0.94 [CI, 0.84 to 1.05]), fatal PE (0.51% vs. 0.40%; odds ratio [OR], 1.30 [CI, 0.77 to 2.18]), or all (fatal and non-fatal) PEs (0.68% vs. 0.83%; OR, 0.82 [CI, 0.55 to 1.21]). The study showed a statistically significant increase in 14-day hemorrhagic stroke or serious extracranial hemorrhage (1.3% vs. 0.80%; OR, 1.73 [CI, 1.22 to 2.46]) and a statistically significant decrease in 14-day recurrent ischemic stroke (2.6% vs. 4.0%; RR, 0.65 [CI, 0.54 to 0.80]).

All Patients Combined

For mortality, PE, and major bleeding events, pooled estimates for medical patients without stroke and patients with acute stroke were very similar. Although the point estimate for the effects on DVT risk was substantially stronger in patients with stroke than in medical patients without stroke, it was too imprecise to draw conclusions about differential risks. Combining evidence from the 2 populations (18 trials; 36 122 participants) showed that heparin was associated with a borderline statistically significant reduction in risk for mortality compared with no heparin prophylaxis (RR, 0.93 [CI, 0.86 to 1.00]; $I^2 = 2\%$; absolute reduction, 6 events per 1000 persons treated [CI, -11 to 0 events]), a statistically significant reduction in risk for PE (RR, 0.70 [CI, 0.56 to 0.87]; $I^2 = 0\%$; absolute reduction, 3 events per 1000 persons treated [CI, 5 to -1 events]), and no statistically significant decrease in symptomatic DVT (RR, 0.75 [CI, 0.43 to 1.30]; absolute reduction, 2 events per 1000 persons treated [CI, -6 to 3 events]). These trials also showed a statistically significant increased risk for all bleeding events (RR, 1.28 [CI, 1.05 to 1.56]; absolute increase, 9 events per 1000 persons treated [CI, 2 to 18 events]) and major bleeding events (RR, 1.61 [CI, 1.23 to 2.10]; $I^2 = 0\%$; absolute increase, 4 events per 1000 persons treated [CI, 1 to 7 events]).

COMPARATIVE EFFECTIVENESS OF LMWH VERSUS UFH

Medical Patients

Nine trials (28–36) ($n = 11\,650$) that compared LMWH with UFH in medical patients showed no statistically significant difference in mortality (RR, 0.91 [CI, 0.73 to 1.13]; $I^2 = 25\%$; absolute reduction, 9 events per 1000 persons treated [CI, -28 to 13 events]) (moderate-quality evidence), PE (RR, 0.70 [CI, 0.44 to 1.11]; $I^2 = 0\%$; absolute reduction, 2 events per 1000 persons treated [CI, -4 to 1 event]) (low-quality evidence), or major bleeding events (RR, 0.89 [CI, 0.70 to 1.15]; $I^2 = 0\%$; absolute reduction, 3 events per 1000 persons treated [CI, -7 to 3 events]) (low-quality evidence).

Acute Stroke

Five trials (37–41) ($n = 2785$) that compared LMWH with UFH in patients with acute stroke did not show statistically significant differences for mortality (RR, 1.00 [CI, 0.81 to 1.22]; $I^2 = 1\%$; absolute reduction, 0 events per 1000 persons treated [CI, -23 to 26 events]) (moderate-quality evidence), symptomatic DVT (RR, 0.34 [CI, 0.11 to 1.00]; absolute reduction, 7 events per 1000 persons treated [CI, -9 to 0 events]) (low-quality evidence), PE (RR, 0.57 [CI, 0.25 to 1.34]; $I^2 = 18\%$; absolute reduction, 4 events per 1000 persons treated [CI, -8 to -3 events]) (low-quality evidence), or major bleeding events (RR, 1.49 [CI, 0.73 to 3.06]; $I^2 = 0\%$; absolute reduction, 4 events per 1000 persons treated [CI, -2 to 19 events]) (low-quality evidence).

All Patients Combined

Evidence from all trials ($n = 14\,435$) comparing LMWH with UFH did not show a statistically significant difference between LMWH and UFH for mortality (RR, 0.94 [CI, 0.82 to 1.08]; $I^2 = 16\%$) or major bleeding events (RR, 0.95 [CI, 0.75 to 1.20]; $I^2 = 0\%$), although a nonsignificant difference favored LMWH for PE (OR, 0.67 [CI, 0.45 to 1.00]; $P = 0.053$; $I^2 = 0\%$).

COMPARATIVE EFFECTIVENESS OF MECHANICAL DEVICES VERSUS NO MECHANICAL DEVICES

Evidence on clinical outcomes from randomized, controlled trials evaluating mechanical devices versus no mechanical devices is sparse. Three trials included in the systematic review compared mechanical devices with no mechanical devices, but 1 large trial ($n = 2518$) included 232 of the 247 deaths reported. It included patients with acute stroke and compared thigh-length graduated compression stockings with no stockings (42). The results showed no statistically significant difference in risk for mortality (RR, 1.11 [CI, 0.87 to 1.42]) (low-quality evidence), symptomatic DVT, or PE. However, risk for lower-extremity skin damage statistically significantly increased among patients treated with compression stockings (RR, 4.02 [CI, 2.34 to 6.91]; absolute increase, 39 events per 1000 patients treated [CI, 17 to 77 events]) (moderate-quality evidence). The 2 other studies showed no differences in rates of PE or mortality (43, 44).

ADDITIONAL EVIDENCE

Four studies met inclusion criteria but could not be meaningfully combined with the studies described because they evaluated different clinical comparisons or interventions. One randomized, controlled trial ($n = 300$) that evaluated LMWH prescribed for different durations in medical patients (45) reported 2 deaths in patients who received LMWH only while immobilized (mean, 5.1 days) compared with no deaths in patients who received LMWH while immobilized and for 10 additional days (mean, 14.5

days) (RR, 0.00). A randomized trial ($n = 90$) of patients who were enrolled at least 7 days after stroke compared LMWH with intermittent pneumatic compression (46). Most patients received heparin prophylaxis before randomization. The study reported 2 symptomatic DVTs and 1 minor bleeding event in the LMWH group compared with no events in the compression group. Another study ($n = 151$) that included patients with acute cerebral hemorrhage compared compression stockings with or without pneumatic compression and found no statistically significant difference in risk for all-cause mortality through 3 months (22% vs. 31%; RR, 0.69 [CI, 0.4 to 1.20]) (47). One symptomatic DVT occurred in each group (RR, 1.04 [CI, 0.07 to 16]) (47). Another study found that proximal DVT occurred more in patients with stroke who wore below-knee stockings than in those who wore thigh-length stockings (48). One study ($n = 6085$) of hospitalized, immobile medical patients who had completed an initial 10-day course of open-label enoxaparin prophylaxis compared an additional 28 days of enoxaparin (40 mg) with placebo (49). After 90 days, the treatment group had a statistically significant reduction in risk for symptomatic VTE (from 28 [1.1%] to 8 [0.3%] events) and an increase in all bleeding events (from 116 [3.9%] to 186 [6.3%] events) and major bleeding events (from 10 [0.3%] to 25 [0.8%] events), with no difference in mortality risk (hazard ratio, 1.04).

SUMMARY

Randomized trials of heparin versus no heparin therapy for medical patients did not show a statistically significant reduction in the risk for mortality or symptomatic DVT and showed an increased risk for bleeding events. However, PE was significantly reduced in medical patients. For patients with acute stroke, heparin increased the risk for major bleeding, with no effect on mortality, symptomatic DVT, or PE. Studies comparing LMWH with UFH did not show any differences in clinical outcomes. Mechanical prophylaxis was not associated with any improvement in clinical outcomes in patients with acute stroke and resulted in an increased risk for lower-extremity skin damage, although evidence on the effects of mechanical prophylaxis was sparse.

RECOMMENDATIONS

Recommendation 1: ACP recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).

The decision to initiate VTE prophylaxis in medical (including stroke) patients should be based on an individualized assessment of the risk for thromboembolism and bleeding, as well as an assessment of the potential harms against modest or even no benefit. Trials that evaluated the

benefits and harms of heparin prophylaxis generally enrolled patients who were considered to be at higher risk for VTE. Risk factors for thromboembolism include presence of inherited conditions—such as factor V Leiden mutation, prothrombin gene mutation, protein S or C deficiency, and antithrombin deficiency—or acquired risk factors—such as surgery, cancer, immobilization, trauma, presence of a central venous catheter, pregnancy, drugs (for example, oral contraceptives, hormone replacement therapy, or tamoxifen), congestive heart failure, chronic renal disease, the antiphospholipid antibody syndrome, obesity, smoking, older age, and history of thromboembolism. Some evidence suggests that heparin is less beneficial in younger patients than in patients older than 75 years (5, 49, 50). Many risk assessment tools are available for estimating thromboembolism risk, but the current evidence is insufficient to recommend a validated tool. Although such instruments may be useful, decisions about heparin prophylaxis may also be based on general evidence regarding the risk factors for VTE and bleeding.

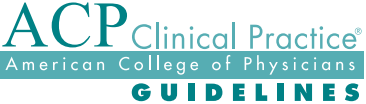
Heparin and related drugs are associated with an increased risk for bleeding. Risk factors for bleeding with anticoagulant therapy include older age; female sex; diabetes; hypertension; presence of cancer; acute or chronic alcoholism; liver disease; severe chronic kidney disease; peptic ulcer disease; anemia; poor treatment adherence; prior stroke or intracerebral hemorrhage; presence of bleeding lesions; bleeding disorder; and concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, antiplatelet agents, antibiotics, statins, fibrates, and steroids.

Recommendation 2: ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).

In hospitalized medical patients, prophylaxis with heparin is associated with a statistically significant reduction in PEs (absolute decrease, 4 events per 1000 persons treated) and increase in all bleeding events (absolute increase, 9 events per 1000 persons treated), a non-statistically significant increase in major bleeding events (absolute increase, 1 event per 1000 persons treated), and no effect on mortality or symptomatic DVT. In most patients, the clinical benefit of reduction of PEs outweighs the harm of increased risk for bleeding events.

In patients with acute stroke, the pooled results from the evidence review showed no statistically significant benefit from heparin prophylaxis on mortality, PE, or symptomatic DVT. The pooled results also showed a statistically significant increase in risk for major bleeding events (absolute increase, 6 events per 1000 persons treated) that outweighed the potential reduction in PEs (absolute decrease, 3 events per 1000 persons treated). However, the pooled results showed wide CIs that also encompassed potential substantial net benefits. Seven of 8 studies that evaluated the effect of heparin on mortality were small (sample size

Figure. Summary of the American College of Physicians' guideline on venous thromboembolism prophylaxis in hospitalized patients.

	
Summary of the American College of Physicians Guideline on Venous Thromboembolism Prophylaxis in Hospitalized Patients	
Disease or condition	VTE
Target audience	Internists, family physicians, other clinicians
Target patient population	Adults with VTE
Interventions	Low-dose heparin products Mechanical devices
Outcomes	Total mortality PE All bleeding Major bleeding
Recommendations	<p><i>Recommendation 1: ACP recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 2: ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 3: ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).</i></p> <p><i>Policy Implication</i> <i>ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal venous thromboembolism prophylaxis regardless of risk.</i></p>
Clinical considerations	<ul style="list-style-type: none"> • This guideline refers to hospitalized medical patients and patients with acute stroke at risk for VTE. • Treatment benefits for VTE are primarily related to reduction in mortality, symptomatic DVT, and PE events. • Assessment of risk for thromboembolism and bleeding is important before initiation of prophylaxis for VTE. • Clinicians who initiate VTE prophylaxis should select heparin (or related) drugs rather than mechanical prophylaxis.

ACP = American College of Physicians; DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

range, 32 to 305 participants) and were published before 1996. Some did not describe use of CT to exclude intracranial hemorrhage before randomization. The strongest evidence in patients with stroke comes from the International Stroke Trial, a large study that randomly assigned 14 578 patients with suspected acute ischemic stroke to receive low-dose (5000 IU twice daily) heparin or no heparin (21). It found no statistically significant differences between low-dose heparin and no heparin in 14-day all-cause mortality, fatal PE, or all (fatal and nonfatal) PEs. Although the risk for hemorrhagic stroke or serious extracranial hemorrhage statistically significantly increased (absolute increase, 5 events per 1000 persons treated), this was offset by a statistically significant and larger decrease in risk for recurrent ischemic stroke (absolute decrease, 14 events per 1000 persons treated). Results of the International Stroke Trial and pooled estimates from patients with stroke were generally consistent with findings from pooled analyses of medical patients without stroke; thus, evidence was insufficient to conclude that risks and benefits of VTE prophylaxis differ between medical patients with stroke

and those without stroke. Evidence on the risks and benefits in patients with stroke is relatively weaker than that in medical patients without stroke, although prevention of recurrent ischemic stroke may be an additional benefit in this population.

The optimal duration of heparin prophylaxis is uncertain. Almost all trials evaluated heparin therapy for patients during hospitalization. A recent study evaluated extended (posthospitalization) heparin therapy for high-risk (immobile) patients (49), but more research is needed to understand the effects of extended therapy on the balance of benefits and harms.

Clinical benefits and harms do not statistically significantly differ between LMWH and UFH. Fondaparinux has not been directly compared with heparin. All prophylactic heparins reviewed for this guideline are administered as subcutaneous injections. The dosage varies from 2 or 3 times daily for UFH to once daily for LMWH or fondaparinux. The average wholesale drug costs are about \$10 per day for UFH, \$35 per day for LMWH (generic enoxaparin is available), and \$60 per day for fondaparinux. In 4

trials that compared UFH with LMWH and assessed heparin-induced thrombocytopenia, 7 cases of heparin-induced thrombocytopenia occurred out of about 1900 in patients receiving UFH and 1 case occurred out of about 1900 patients receiving LMWH ($P = 0.07$) (29, 31, 33, 37). Hence, the choice of agent for prophylaxis of VTE should be based on ease of use, adverse effect profile, and cost of medication.

Recommendation 3: ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).

Mechanical prophylaxis with graduated compression stockings was not effective in preventing VTE or reducing mortality and resulted in clinically important lower-extremity skin damage. Clinicians who initiate VTE prophylaxis should select heparin (or related drugs) rather than graduated compression stockings for patients in whom heparin can be used. In patients at high risk for bleeding events or in whom heparin is contraindicated for other reasons, intermittent pneumatic compression may be a reasonable option, because evidence suggests that it is beneficial in surgical patients. However, intermittent pneumatic compression has not been sufficiently evaluated as a stand-alone intervention in medical patients to reliably estimate benefits and harms.

See the **Figure** for a summary of the recommendations and clinical considerations.

POLICY IMPLICATION

ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal venous thromboembolism prophylaxis regardless of risk.

In the United States, many organizations have developed performance measures intended to increase the appropriate use of VTE prophylaxis in hospitalized patients. However, in some clinical settings, performance measures have been based on rates of VTE prophylaxis in all patients, regardless of their underlying risk. The evidence reviewed for the clinical recommendations in this guideline does not support routine prophylaxis of VTE in all medical patients and emphasizes the tradeoff in harms and benefits. Clinicians caring for these patients must assess the risks and benefits before deciding whether to initiate prophylaxis. In some cases, not prescribing VTE prophylaxis may be justified because the estimated tradeoff between potential risks and benefits is small or unclear. Because no standard, accepted formula for risk assessment exists to identify which medical patients are likely to benefit from VTE prophylaxis, the decision is best left to physician judgment, and performance measures targeting all patients are inappropriate. Until we can better identify patients who truly benefit, performance measures that encourage VTE prophylaxis for all medical patients may encourage physicians

to use prophylaxis in low-risk patients for whom the risks may exceed the benefit.

From the American College of Physicians, Philadelphia, Pennsylvania; Oregon Health & Science University, Portland, Oregon; and West Los Angeles Veterans Affairs Medical Center, Los Angeles, California.

Note: Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians’ judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the U.S. Department of Veterans Affairs.

Acknowledgment: The authors thank the ACP Performance Measurement Committee for its review of and comments on the manuscript.

Financial Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Potential Conflicts of Interest: Any financial and nonfinancial conflicts of interest of the group members were declared, discussed, and resolved. Dr. Humphrey: *Consultancy:* U.S. Preventive Services Task Force. *Royalties:* UpToDate. Dr. Shekelle: *Consultancy:* ECRI Institute; *Employment:* Department of Veterans Affairs; *Grants/grants pending (money to institution):* Agency for Healthcare Research and Quality, Department of Veterans Affairs, Centers for Medicare & Medicaid Services; *Royalties:* UpToDate. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1931.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

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

References

- Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:338S-400S. [PMID: 15383478]
- Qaseem A, Snow V, Barry P, Hornbake ER, Rodnick JE, Tobolic T, et al; Joint American Academy of Family Physicians/American College of Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med*. 2007;146:454-8. [PMID: 17371890]
- Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. *BMJ*. 1991;302:709-11. [PMID: 2021744]
- Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med*. 1989;82:203-5. [PMID: 2716016]
- Ali Khan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol*. 2004;57:1254-7. [PMID: 15563663]
- Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and

- case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med.* 1991;151:933-8. [PMID: 2025141]
7. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158:585-93. [PMID: 9521222]
 8. Lederle FA, Zylla D, MacDonald R, Wilt T. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: background review for an American College of Physicians clinical practice guideline. *Ann Intern Med.* 2011;155:602-615.
 9. Qaseem A, Snow V, Owens DK, Shekelle P; **Clinical Guidelines Committee of the American College of Physicians.** The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med.* 2010;153:194-9. [PMID: 20679562]
 10. Weber C, Merminod T, Herrmann FR, Zulian GB. Prophylactic anticoagulation in cancer palliative care: a prospective randomised study. *Support Care Cancer.* 2008;16:847-52. [PMID: 17940809]
 11. Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR. Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J.* 1981;26:115-7. [PMID: 7291971]
 12. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al; **ARTEMIS Investigators.** Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ.* 2006;332:325-9. [PMID: 16439370]
 13. Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. *Haemostasis.* 1986;16:159-64. [PMID: 3710294]
 14. Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med.* 2000;161:1109-14. [PMID: 10764298]
 15. Gärdlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. *Lancet.* 1996;347:1357-61. [PMID: 8637340]
 16. Lederle FA, Sacks JM, Fiore L, Landefeld CS, Steinberg N, Peters RW, et al. The prophylaxis of medical patients for thromboembolism pilot study. *Am J Med.* 2006;119:54-9. [PMID: 16431185]
 17. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ; **PREVENT Medical Thromboprophylaxis Study Group.** Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation.* 2004;110:874-9. [PMID: 15289368]
 18. Mahé I, Bergmann JF, d'Azémar P, Vaissie JJ, Caulin C. Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. *Eur J Clin Pharmacol.* 2005;61:347-51. [PMID: 15981008]
 19. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med.* 1999;341:793-800. [PMID: 10477777]
 20. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. *Klin Wochenschr.* 1988;66:1182-3. [PMID: 3062268]
 21. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *International Stroke Trial Collaborative Group. Lancet.* 1997;349:1569-81. [PMID: 9174558]
 22. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Engl J Med.* 1995;333:1588-93. [PMID: 7477193]
 23. McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. *Age Ageing.* 1986;15:84-8. [PMID: 3962762]
 24. McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, Macey DJ. Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. *Lancet.* 1977;2:800-1. [PMID: 71605]
 25. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. *Haemostasis.* 1989;19:245-50. [PMID: 2550335]
 26. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. *Semin Thromb Hemost.* 1990;16 Suppl:25-33. [PMID: 1962901]
 27. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al. Double-blind randomised trial of Org 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. *Lancet.* 1987;1:523-6. [PMID: 2434815]
 28. Aquino JP, Gambier A, Ducros JJ. Prophylaxis of thromboembolic disorders in elderly patients with fraxiparine. In: Bounameaux H, Samama M, ten Cate JW, eds. *Fraxiparine: Second International Symposium Recent Pharmacological and Clinical Data.* Hoboken, NJ: J Wiley; 1991.
 29. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. *Thromb Haemost.* 1996;76:529-34. [PMID: 8902991]
 30. Harenberg J, Kallenbach B, Martin U, Dempfle CE, Zimmermann R, Kübler W, et al. Randomized controlled study of heparin and low molecular weight heparin for prevention of deep-vein thrombosis in medical patients. *Thromb Res.* 1990;59:639-50. [PMID: 2173168]
 31. Harenberg J, Roebuck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. *Haemostasis.* 1996;26:127-39. [PMID: 8738587]
 32. Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW; **THE-PRINCE Study Group.** Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J.* 2003;145:614-21. [PMID: 12679756]
 33. Lechler E, Schramm W, Flosbach CW. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. *Haemostasis.* 1996;26 Suppl 2:49-56. [PMID: 8707167]
 34. Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, et al; **PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group.** Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med.* 2011;364:1305-14. [PMID: 21417952]
 35. Riess H, Haas S, Tebbe U, Gerlach HE, Abletshauer C, Sieder C, et al. A randomized, double-blind study of certoparin vs. unfractionated heparin to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY Study. *J Thromb Haemost.* 2010;8:1209-15. [PMID: 20218984]
 36. Schellong SM, Haas S, Greinacher A, Schwanebeck U, Sieder C, Abletshauer C, et al. An open-label comparison of the efficacy and safety of certoparin versus unfractionated heparin for the prevention of thromboembolic complications in acutely ill medical patients: CERTAIN. *Expert Opin Pharmacother.* 2010;11:2953-61. [PMID: 20950224]
 37. Diener HC, Ringelstein EB, von Kummer R, Landgraf H, Koppenhagen K, Harenberg J, et al; **PROTECT Trial Group.** Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke.* 2006;37:139-44. [PMID: 16306456]
 38. Dumas R, Woitinas F, Kutnowski M, Nikolic I, Berberich R, Abedinpour F, et al. A multicentre, double-blind, randomized study to compare the safety and efficacy of once-daily ORG 10172 and twice-daily low-dose heparin in preventing deep-vein thrombosis in patients with acute ischaemic stroke. *Age Ageing.* 1994;23:512-6. [PMID: 9231947]
 39. Hillbom M, Eirilä T, Sotaniemi K, Tatlisumak T, Sarna S, Kaste M. Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. *Acta Neurol Scand.* 2002;106:84-92. [PMID: 12100367]
 40. Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, et al; **PREVAIL Investigators.** The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet.* 2007;369:1347-55. [PMID: 17448820]

41. Turpie AG, Gent M, Côte R, Levine MN, Ginsberg JS, Powers PJ, et al. A low-molecular-weight heparinoid compared with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke. A randomized, double-blind study. *Ann Intern Med.* 1992;117:353-7. [PMID: 1503326]
42. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al; CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet.* 2009;373:1958-65. [PMID: 19477503]
43. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *QJM.* 2000;93:359-64. [PMID: 10873185]
44. Prasad BK, Banerjee AK, Howard H. Incidence of deep vein thrombosis and the effect of pneumatic compression of the calf in elderly hemiplegics. *Age Ageing.* 1982;11:42-4. [PMID: 7072559]
45. Luba M, Firek A, Kochanowski Z. [Two models of thromboprophylaxis in acutely ill medical inpatients]. *Pol Arch Med Wewn.* 2007;117:31-7. [PMID: 17722473]
46. Green D, Akuthota V, Eiken M, Feinglass J, Fuller S, Hwang C, et al. Prevention of thromboembolism in stroke rehabilitation patients. *Top Stroke Rehabil.* 1998;5:68-74.
47. Licut K, Bressollette L, Le Gal G, Etienne E, De Tinteniak A, Renault A, et al; VICTORIAh (Venous Intermittent Compression and Thrombosis Occurrence Related to Intra-cerebral Acute hemorrhage) Investigators. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. *Neurology.* 2005;65:865-9. [PMID: 16186525]
48. CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med.* 2010;153:553-62. [PMID: 20855784]
49. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Nicol P, et al; EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med.* 2010;153:8-18. [PMID: 20621900]
50. Kucher N, Leizorovicz A, Vaitkus PT, Cohen AT, Turpie AG, Olsson CG, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. *Arch Intern Med.* 2005;165:341-5. [PMID: 15710801]

DOWNLOAD IMPORTANT REFERENCES TO CITATION MANAGERS

At www.annals.org, article citations may be directly downloaded to any of the following formats: EndNote, Reference Manager, ProCite, BibTex, RefWorks, or Medlars.

Current Author Addresses: Drs. Qaseem and Starkey: 190 N. Independence Mall West, Philadelphia, PA 19106.

Dr. Chou: 3181 SW Sam Jackson Park Road, Mail Code: BICC, Portland, OR 97239.

Dr. Humphrey: 3710 SW US Veterans Hospital Road, Portland, OR 97201.

Dr. Shekelle: 11301 Wilshire Boulevard, Los Angeles, CA 90073.

Author Contributions: Conception and design: A. Qaseem.

Analysis and interpretation of the data: A. Qaseem, R. Chou, L.L. Humphrey, P. Shekelle.

Drafting of the article: A. Qaseem, R. Chou, M. Starkey.

Critical revision of the article for important intellectual content: A. Qaseem, R. Chou, L.L. Humphrey, P. Shekelle.

Final approval of the article: A. Qaseem, R. Chou, L.L. Humphrey, M. Starkey, P. Shekelle.

Statistical expertise: A. Qaseem.

Administrative, technical, or logistic support: A. Qaseem, M. Starkey.

Collection and assembly of data: A. Qaseem, M. Starkey.