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Benefits of more aggressive VTE prophylaxis in hospitalized medical patients

■ ABSTRACT

Venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism, is a well-known risk in surgical patients, but it is also a significant and often unrecognized source of mortality and morbidity in hospitalized medical patients. The need for routine prophylaxis in the general medical population is increasingly supported.

■ KEY POINTS

Evidence-based consensus guidelines call for prophylactic treatment of hospitalized patients to reduce the morbidity and mortality associated with VTE.

Prophylaxis is often not given or is given in subtherapeutic regimens despite consensus treatment guidelines.

New strategies for treatment, such as local guidelines with computerized reminder systems, may increase the effective use of prophylactic treatment and thus reduce the mortality and morbidity associated with VTE in hospitalized medical patients.

Improved anticoagulant drugs, with convenient oral dosing and without the need for frequent laboratory monitoring, may also reduce the burden of VTE.

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This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

MANY HOSPITALIZED medical patients should be receiving treatment to prevent venous thromboembolism (VTE, which includes deep venous thrombosis and pulmonary embolism), according to emerging evidence and consensus guidelines from the American College of Chest Physicians and other organizations.^{1,2}

Although when we think of VTE we usually think of surgical patients, up to 60% of cases of VTE actually occur in hospitalized medical patients.^{3,4}

This review discusses the need for VTE prophylaxis in medical patients and explores practical methods to make sure that this at-risk population actually receives it.

■ RATIONALE FOR VTE PROPHYLAXIS FOR HOSPITALIZED PATIENTS

The premise for prophylaxis rests on three principles:

- Patients likely to develop VTE can be identified by their risk factors
- The consequences of VTE can be severe and irreversible
- Available methods of prophylaxis are effective and safe in preventing VTE in hospitalized patients.

VTE risk is predictable

In hospitalized patients, the combination of prolonged immobility and severe disease makes VTE a common complication.^{5,6} The characteristics associated with VTE are well established.

TABLE 1

Clinical risk factors for venous thromboembolism in medical patients

Patient-related

Increasing age
 Prolonged immobility (eg, hospital or nursing home confinement)
 Male sex
 Obesity
 Cigarette smoking
 Long-distance travel
 Inherited thrombophilias
 Antithrombin III deficiency
 Protein C deficiency
 Protein S deficiency
 Factor V Leiden mutation
 Risk factors in women
 Pregnancy
 Oral contraceptives
 Hormone replacement therapy
 Prior venous thrombosis
 Prior superficial venous thrombosis and varicose veins

Condition-related

Indwelling central venous catheter
 Paralysis of lower limbs
 Medical illnesses
 Malignancy
 Congestive heart failure
 Myocardial infarction
 Stroke with paresis
 Nephrotic syndrome
 Infection
 Inflammatory bowel disease
 Polycythemia

VTE most often accompanies serious illness and rarely develops in healthy, active people.^{5,7} A retrospective review of medical records in Olmsted County, MN, between 1980 and 1990 demonstrated a strong association between hospitalization and the development of deep venous thrombosis.⁵ The average annual incidence of inpatient VTE, adjusted for age and sex, was 960.5 per 10,000 person-years, compared with 7.1 per 10,000 person-years in patients in the community.⁵

In the intensive care unit, 9% to 32% of medical and surgical patients develop deep venous thrombosis (diagnosed by either ultrasonography or fibrinogen scanning) within 1 week of admission.⁸

The risk of VTE, particularly of pulmonary embolism, increases with age.⁵ Other risk factors are related to in-hospital procedures or medical conditions (TABLE 1). A retrospective study in 16 acute care hospitals found that 78% of 1,000 hospitalized patients had at least one risk factor for VTE and 48% had two or more risk factors.⁹

A method for risk assessment recommended by the Thromboembolic Risk Factors (THRIFT II) consensus group stratifies patients as being at low, moderate, or high risk (TABLE 2).¹⁰ Greater risk indicates a greater need for prophylaxis.

VTE has serious consequences

The most severe consequence of VTE is death from pulmonary embolism. An autopsy study showed that pulmonary embolism accounted for 7% of all deaths during hospitalization.¹¹ Of the patients who died of pulmonary embolism, 59% were medical patients. In a subsequent prospective study,¹¹ approximately 1 in 20 medical patients who died during hospitalization died of pulmonary embolism.

After a pulmonary embolism, the 3-month mortality rate ranges from 15% to 18%,¹² and the survival rate at 1 year is as low as 59%.¹³

Patients who survive the initial event are at high risk of recurrence. The cumulative incidence of recurrent venographically confirmed VTE is 18% after 2 years, and the incidence of postthrombotic syndrome (with symptoms that include pain, cramps, edema, redness, and/or ulceration) is 22.8% after 2 years.¹⁴

Waiting for VTE to develop and then treating it is not acceptable.^{14,15} VTE can have nonspecific or minimal symptoms, and therefore it can be difficult to diagnose,^{16,17} especially in critically ill patients, in whom the prevalence of venographically detectable VTE is as high as 80%.³ In addition, diagnostic tests for VTE are expensive, and their sensitivity is highly variable.¹⁸

Furthermore, in more than one third of VTE deaths, the VTE was clinically unrecognized.¹³ The greatest risk of death from pulmonary embolism occurs within an hour after the thrombus reaches the lung, allowing little time for treatment.⁷

**TABLE 2****Categories of risk for venous thromboembolism in medical patients**

RISK LEVEL	RISK RATES		PATIENT GROUP
	DEEP VENOUS THROMBOSIS	FATAL PULMONARY EMBOLISM	
Low	< 10%	0.01%	Minor trauma or medical illness
Moderate	10%–40%	0.1%–1%	Major medical illness (ie, heart or lung disease, cancer, inflammatory bowel disease)
High	40%–80%	1%–10%	Major illness in patients with previous deep venous thrombosis, pulmonary embolism, or thrombophilia (see TABLE 1)

MODIFIED FROM THE SECOND THROMBOEMBOLIC RISK FACTORS (THRIFT II) CONSENSUS GROUP. RISK OF AND PROPHYLAXIS FOR VENOUS THROMBOEMBOLISM IN HOSPITAL PATIENTS. PHLEBOLOGY 1998; 13:87–97, WITH THE PERMISSION OF THE ROYAL SOCIETY OF MEDICINE PRESS, LONDON.

Prophylaxis is effective

Randomized, controlled clinical trials indicate that available methods to prevent VTE are beneficial in surgical patients. Unfortunately, most of the studies done in medical patients were small, were performed in heterogeneous populations, had methodological problems (mostly selection bias, randomization bias, and limitations of outcomes measures), or produced inconsistent results,^{19–28} introducing severe limitations to the published meta-analytical studies.^{21,29}

Even in large studies with clinically significant outcomes such as death, no difference in clinical outcomes can be found when patients receive subcutaneous injections of unfractionated heparin 5,000 units twice a day vs placebo.^{20,28} Therefore, given the stated limitations, prophylactic regimens such as subcutaneous unfractionated heparin 5,000 units twice a day should be considered inappropriate.

On the other hand, one meta-analysis³⁰ suggested that low-molecular-weight heparin reduced the risk of deep venous thrombosis by 72% compared with placebo ($P < .001$), with similar reductions in risk of clinical pulmonary embolism (75% reduction, $P = 0.018$) and clinical VTE (71% reduction, $P = .009$).

MEDENOX trial. The Medical Patients With Enoxaparin (MEDENOX) trial confirmed that hospitalized medical patients at moderate risk for developing VTE benefit from prophylactic therapy with low-molecular-weight heparin.^{31–33}

This phase 3, double-blind, multicenter trial randomized 1,102 medical patients to receive enoxaparin (Lovenox) 20 or 40 mg subcutaneously once a day or placebo once a day. The duration of treatment was 10 plus or minus 4 days. Patients were 40 years of age or older, were hospitalized 6 or more days, and had one or more common admitting medical diagnoses such as heart failure (New York Heart Association [NYHA] class III or IV), acute respiratory failure, acute infection, rheumatologic disorders, or inflammatory bowel disease. The primary outcome was venographically confirmed VTE between days 1 and 14 of treatment and at follow-up of up to 110 days.

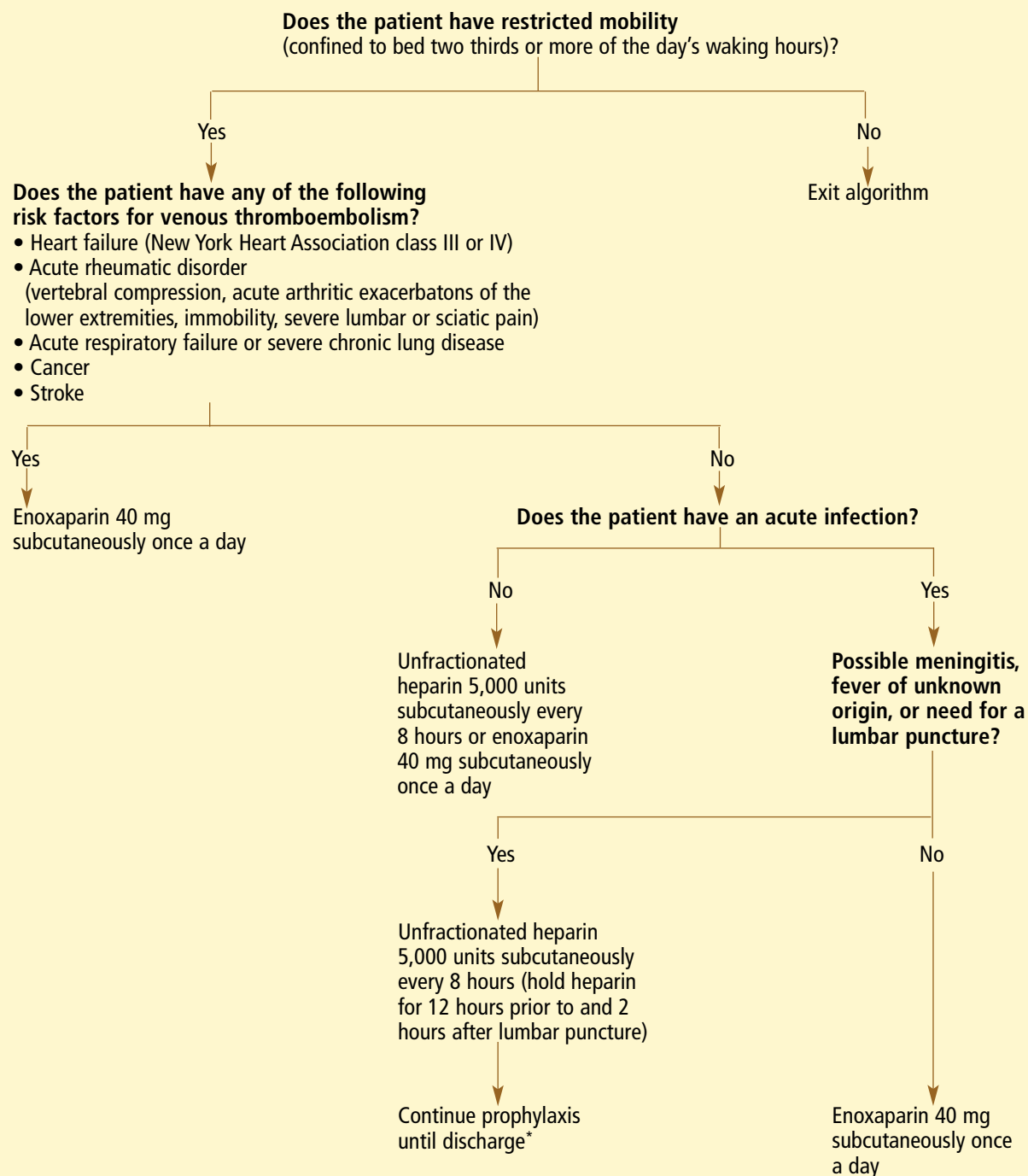
At 14 days, the incidence of VTE was 14.9% in the placebo group, 15.5% in the enoxaparin 20 mg group, and 5.5% in the enoxaparin 40 mg group ($P < .001$ vs placebo). The pattern was similar on long-term follow-up.^{31,32} The lack of efficacy of enoxaparin 20 mg in this study could be explained by the severity of illness in the study population. The 20-mg dose should perhaps be safe for patients with medical illnesses that pose low to low-moderate risk.

EXCLAIM study. The ongoing Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) study will further clarify the benefits of long-term VTE prophylaxis after discharge in medical patients.³⁴

PRINCE studies. The Thromboembolic Prevention in Cardiopulmonary Diseases With Enoxaparin (PRINCE) studies com-

Up to 1/3 of ICU patients develop deep venous thrombosis within 1 week

Thomas Jefferson Medical College protocol for venous thromboembolism prophylaxis in medically ill patients



*Extended prophylaxis may be considered for patients with continued restricted mobility and risk factors for VTE.

FIGURE 1



pared the efficacy of enoxaparin 40 mg once a day vs unfractionated heparin 5,000 units three times a day in patients with severe respiratory disease or NYHA class III or IV heart failure.^{35,36} The incidence of VTE was 16.1% in congestive heart failure patients given unfractionated heparin vs 9.7% with enoxaparin. Although the difference was not statistically significant, it suggests that low-molecular-weight heparin may be more clinically effective than unfractionated heparin in these patients. There was no statistical or clinical difference between treatments in the patients with respiratory disease.

PREVENT. The Prospective Evaluation of Dalteparin Efficacy in Immobilized Patients trial (PREVENT) compared dalteparin (Fragmin) 5,000 units once a day vs placebo in patients with severe respiratory disease (30%), heart failure (52%), or other acute medical illnesses.³⁷ The results indicate that the incidence of “clinically important VTE” (defined as objectively verified symptomatic deep venous thrombosis, pulmonary embolism, sudden death, or objectively verified asymptomatic proximal deep venous thrombosis) was 4.96% in the placebo group vs 2.77% in the dalteparin group.

ARTEMIS study. In the Arixtra for ThromboEmbolism Prevention in a Medical Indications study (ARTEMIS), fondaparinux (Arixtra), a synthetic selective indirect factor Xa inhibitor, given at dose of 2.5 mg subcutaneously once a day, significantly reduced the risk of VTE in acutely ill hospitalized medical patients. The reported absolute incidence in the intervention group was 5.6% compared with 10.5% in the placebo group.³⁸

Limited data on mechanical prophylaxis. Data are limited on the use of mechanical prophylaxis such as elastic stockings or pneumatic compression boots. Mechanical prophylaxis has been extensively studied in surgical populations and it is recommended for patients at lower risk for VTE.¹ It is reasonable to consider mechanical prophylaxis in a patient in whom DVT prophylaxis is indicated who has a contraindication to anticoagulation.

VTE prophylaxis with anticoagulants is safe

Bleeding is the most common adverse event during VTE prophylaxis with anticoagulants.

However, clinical trials showed no difference in the incidence of major bleeding with the use of anticoagulant drugs for VTE prophylaxis vs placebo.^{31–38} Similarly, a study found no increase in major bleeding with long-term use of low-molecular-weight heparin after surgery vs placebo.³⁹

It seems reasonable to extrapolate bleeding risk from surgical to medical patients and state that certain conditions such as prior history of gastrointestinal bleeding, metastatic cancer, or mild thrombocytopenia do not constitute contraindications for prophylactic pharmacological anticoagulation.

To decrease the risk of bleeding during invasive procedures, patients receiving prophylaxis with unfractionated heparin should have the medication withheld starting approximately 8 hours before the procedure; those receiving low-molecular weight heparin should have it withheld 12 hours.⁴⁰

EVIDENCE-BASED GUIDELINES FOR THROMBOPROPHYLAXIS

The American College of Chest Physicians (ACCP) strongly supports the use of VTE prophylaxis in hospitalized patients and has developed evidence-based guidelines for clinicians.¹

ACCP guidelines in medical patients

VTE prophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin is recommended for patients with risk factors such as bed rest, cancer, heart failure, or severe lung disease. Most patients in intensive care should be given pharmacologic prophylaxis for VTE.¹ Aspirin is not recommended for VTE prophylaxis because other measures are more effective.¹

Development of local protocols

The ACCP recommends that hospitals develop local written protocols to ensure that all hospitalized patients receive appropriate and adequate prophylaxis.¹ Pre-printed or computerized forms should be available. Such an approach has been successfully implemented at our institution (FIGURE 1).

The ACCP strongly supports VTE prophylaxis and has issued guidelines

■ PROPHYLAXIS FOR VTE IS OFTEN INADEQUATE

Although formal guidelines have been published, pulmonary embolism is still the most common preventable cause of death in hospitalized patients, causing or contributing to 5% to 10% of all in-hospital deaths.¹¹

A cohort study performed at a large teaching hospital⁴¹ determined that one sixth of all cases of VTE could have been prevented had physicians followed the ACCP guidelines. The potentially preventable cases of VTE represented two thirds of all VTE cases for which prophylaxis had been indicated. The most common causes of inadequate prophylaxis were failure to give any prophylaxis at all (47.7%), inadequate duration (22.7%), or incorrect type of prophylaxis (20.5%). This study suggests that both underused prophylaxis and subtherapeutic prophylaxis are causes for concern.

Medical patients are the most seriously undertreated, with estimated prophylaxis rates of less than 20% in populations who should be receiving it according to guidelines.^{36,41}

Fewer than 20% of medical patients who should be getting VTE prophylaxis are getting it

Reasons for inadequate prophylaxis

Physicians may not be prescribing adequate prophylaxis for several reasons.

Underestimation of the problem. Venous thromboembolism and pulmonary embolism can be difficult to identify on the basis of history and physical findings, even in patients at high risk. In a patient recovering from a severe illness, the symptoms and signs of VTE may be unnoticed, ignored, or attributed to other conditions.^{16,42} Similarly, pulmonary embolism is often called “the great masquerader,” as its symptoms, including dyspnea, anxiety, or chest pain, are also symptoms of many other conditions.^{16,42} Although a significant proportion of clinically significant pulmonary embolisms result from deep venous thrombosis of the lower extremities, only one third of patients with pulmonary embolism have clinical signs of deep venous thrombosis.¹⁶

Because VTE is so hard to diagnose, physicians may not associate later sequelae (morbidity or mortality) with the initial episode of VTE.

Overestimation of bleeding risk. The benefits of anticoagulation may be underesti-

mated, but the bleeding risk may be overestimated. Carefully controlled doses of the most common anticoagulants used to prevent VTE do not significantly increase the overall risk for major bleeding,^{30,31,43–45} This small increase in risk is less than the risk of VTE or pulmonary embolism in most patients, and most bleeding incidents are more easily resolved than an episode of pulmonary embolism.

Mistrust of the guidelines. Physicians may not trust guidelines that are based on evidence they consider incomplete. Awareness of available studies in medical patients, such as MEDENOX and PRINCE, may improve compliance with the guidelines.

Concerns about cost. Some doctors may be concerned about the cost-effectiveness of VTE prophylaxis. However, in the MEDENOX trial, additional drug costs were offset by reductions in other costs, particularly hospitalization.⁴⁶

Inconvenience. Current methods of prophylaxis are often uncomfortable or inconvenient for the patient. Low-dose unfractionated heparin and low-molecular-weight heparin are given by injection. In the PRINCE and PRIME studies, the reported incidences of injection-site hematoma were 1.2% and 4.6% with enoxaparin vs 3.3% and 10.8% with unfractionated heparin, respectively. In a long-term outpatient study,³⁹ 16% of patients given dalteparin reported bruising at the injection site.

Although warfarin is given orally, it requires regular blood testing and frequent dose adjustment. Furthermore, its frequent interactions with other medications must be carefully managed. Under use of prophylaxis, particularly after hospital discharge, may be associated with these practical issues.

■ STRATEGIES FOR INCREASING THROMBOPROPHYLAXIS

Local support

Local protocols may improve appropriate implementation of VTE prophylaxis. For example, the protocol used at Thomas Jefferson University Hospital calls for VTE prophylaxis for any patient with restricted mobility (FIGURE 1). Computerized reminder



systems further facilitate appropriate use of prophylaxis by incorporating protocols into admission orders and providing periodic reminders.⁴⁷

More convenient anticoagulant medications

Oral anticoagulant agents that avoid the pain and bruising associated with injections but do not require coagulation monitoring are in development. Several oral anticoagulants have been evaluated in clinical trials to prevent VTE in orthopedic surgery patients, including sodium *N*-[8(-2-hydroxybenzoyl) amino] caprylate (SNAC)-heparin, a formulation combining heparin with a carrier molecule for oral absorption, and ximelagatran (Exanta), an oral direct thrombin inhibitor.^{34,48–50}

The Prophylaxis With Oral Heparin Emisphere SNAC Against Thromboembolic Complications trial (PROTECT) found that

SNAC-heparin reduced the incidence of VTE following total hip replacement surgery but was not more effective than enoxaparin.³⁴ Nevertheless, oral dosage forms of heparin may be useful after further refinement.

In contrast, phase 2 and phase 3 studies have demonstrated that ximelagatran 24 mg twice a day is at least as effective in preventing VTE after orthopedic surgery as dalteparin, enoxaparin, or warfarin,^{48,50–52} and ximelagatran 36 mg twice a day is superior to enoxaparin.⁵³ Ximelagatran was well tolerated and did not require coagulation monitoring, and bleeding rates were similar to those with the comparison drugs.^{48,49,51}

Concerns remain, however, with the appreciable (6.4%) incidence of liver function test elevations observed with the drug. Further studies will be needed to assess its safety, especially with long-term treatment regimens.



REFERENCES

- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. *Chest* 2004; 126:3385–400S.
- Bick RL, Haas SK. International consensus recommendations. Summary statement and additional suggested guidelines. European Consensus Conference, November 1991. American College of Chest Physicians consensus statement of 1995. International Consensus Statement, 1997. *Med Clin North Am* 1998; 82:613–633.
- Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest* 2000; 118:1680–1684.
- Centers for Disease Control and Prevention/National Center for Health Care Statistics. National Hospital Discharge Survey, 1997. Centers for Disease Control. Available at: www.cdc.gov/nchs. Accessed January 6, 2003.
- Heit JA, Melton LJ, 3rd, Lohse CM, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. *Mayo Clin Proc* 2001; 76:1102–1110.
- Kim V, Spandorfer J. Epidemiology of venous thromboembolic disease. *Emerg Med Clin North Am* 2001; 19:839–859.
- Alpert JS, Dalen JE. Epidemiology and natural history of venous thromboembolism. *Prog Cardiovasc Dis* 1994; 36:417–422.
- Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001; 161:1268–1279.
- Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. *Arch Intern Med* 1992; 152:1660–1664.
- Second Thromboembolic Risk Factors (THRIFT II) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Phlebology* 1998; 13:87–97.
- Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. *J Clin Pathol* 1997; 50:609–610.
- Goldhaber SZ. Pulmonary embolism. *N Engl J Med* 1998; 339:93–104.
- Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; 159:445–453.
- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125:1–7.
- Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc* 2000; 75:1249–1256.
- Tanios MA, Simon AR, Hassoun PM. Management of venous thromboembolic disease in the chronically critically ill patient. *Clin Chest Med* 2001; 22:105–122.
- Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353:1386–1389.
- Agnelli G, Taliani MR, Verso M. Building effective prophylaxis of deep vein thrombosis in the outpatient setting. *Blood Coagul Fibrinolysis* 1999; 10(suppl 2):S29–S35.
- 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; 26:115–117.
- Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. *Ann Intern Med* 1982; 96:561–565.
- Cade JF. High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982; 10:448–450.
- Cade JF, Andrews JT, Stubbs AE. Comparison of sodium and calcium heparin in prevention of venous thromboembolism. *Aust N Z J Med* 1982; 12:501–504.
- Dahan R, Houlbert D, Caulin C, 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; 16:159–164.
- Ibarra-Perez C, Lau-Cortes E, Colmenero-Zubiate S, et al. Prevalence and prevention of deep venous thrombosis of the lower extremities in high-risk pulmonary patients. *Angiology* 1988; 39:505–513.
- Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. *Haemostasis* 1996; 26:127–139.
- 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.
27. **Bergmann JF, Neuhaert 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; 76:529–534.
 28. **Gardlund 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; 347:1357–1361.
 29. **Mismetti P, Laporte-Simitsidis S, Tardy B, et al.** Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; 83:14–19.
 30. **Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H.** Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; 88:913–930.
 31. **Samama MM, Cohen AT, Darmon JY, 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.
 32. **Cohen AT, Zaw HM, Alikhan R.** Benefits of deep-vein thrombosis prophylaxis in the nonsurgical patient: The MEDENOX trial. *Semin Hematol* 2001; 38(suppl 5):31–38.
 33. **Turpie AG.** Thrombosis prophylaxis in the acutely ill medical patient: insights from the prophylaxis in medical patients with enoxaparin (MEDENOX) trial. *Am J Cardiol* 2000; 86(12 suppl 2):48–52.
 34. **Hull RD, Kakkar AK, Marder VJ, Pineo GF, Goldberg MM, Raskob GE.** Oral-SNAC heparin vs. enoxaparin for preventing venous thromboembolism following total hip replacement (abstract 558). *Blood* 2002; 100:148a–149a.
 35. **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; 145:614–621.
 36. **Cohen AT, Alikhan R.** Prophylaxis of venous thromboembolism in medical patients. *Curr Opin Pulm Med* 2001; 7:332–337.
 37. **Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ.** Randomized placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; 110:874–879.
 38. **Cohen AT, Gallus AS, Lassen MR, et al.** Fondaparinux vs placebo for the prevention of venous thromboembolism in acutely ill medical patients (ARTEMIS). Program and abstracts of the XIX Congress of the International Society on Thrombosis and Haemostasis; Birmingham, UK, July 12–13, 2003. P2406.
 39. **Hull RD, Pineo GF, Francis C, et al.** Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. North American Fragmin Trial Investigators. *Arch Intern Med* 2000; 160:2208–2215.
 40. **Dunn AS, Turpie AG.** Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med* 2003; 163:901–908.
 41. **Arnold DM, Kahn SR, Shrier I.** Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. *Chest* 2001; 120:1964–1971.
 42. **Goldhaber SZ, Visani L, De Rosa M.** Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353:1386–1389.
 43. **Eikelboom JW, Quinlan DJ, Douketis J.** Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. *Lancet* 2001; 358:9–15.
 44. **Freedman KB, Brookenthal KR, Fitzgerald RH, Jr., Williams S, Lonner JH.** A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am* 2000; 82-A:929–938.
 45. **Kuijjer PM, Hutten BA, Prins MH, Buller HR.** Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999; 159:457–460.
 46. **Nuijten MJ, Berto P, Kosa J, Nadipelli V, Cimminiello C, Spreafico A.** Cost-effectiveness of enoxaparin as thromboprophylaxis in acutely ill medical patients from the Italian NHS perspective. *Recenti Prog Med* 2002; 93:80–91.
 47. **Audet AM, Anderson FA, St John R.** The prevention of venous thromboembolism: a statewide evaluation of practices in Massachusetts. *Therapie* 1998; 53:591–594.
 48. **Francis CW, Davidson BL, Berkowitz SD, et al.** Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. A randomized, double-blind trial. *Ann Intern Med* 2002; 137:648–655.
 49. **Eriksson BI, Agnelli G, Cohen AT, et al.** The direct thrombin inhibitor melagatran, followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. *J Thromb Haemost* 2003; 1:2490–2496.
 50. **Francis CW, Berkowitz SD, Comp PC, et al.** Comparison of Ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003; 349:1703–1712.
 51. **Eriksson BI, Bergqvist D, Kaleb P, et al.** Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomized trial. *Lancet* 2002; 360:1441–1447.
 52. **Colwell CW, Berkowitz SD, Davidson BL, et al.** Randomized, double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and enoxaparin to prevent venous thromboembolism (VTE) after total hip arthroplasty (THA) (abstract 2952). *Blood* 2001; 98:706a.
 53. **PRNewswire-FirstCall.** Emisphere Technologies reports results from phase III oral heparin PROTECT trial. Emisphere Technologies. Available at: <http://www.emisphere.com/new/home.htm>. Accessed June 4, 2002.

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