REVIEW

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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 oganizations.[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-analysis[30] 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.

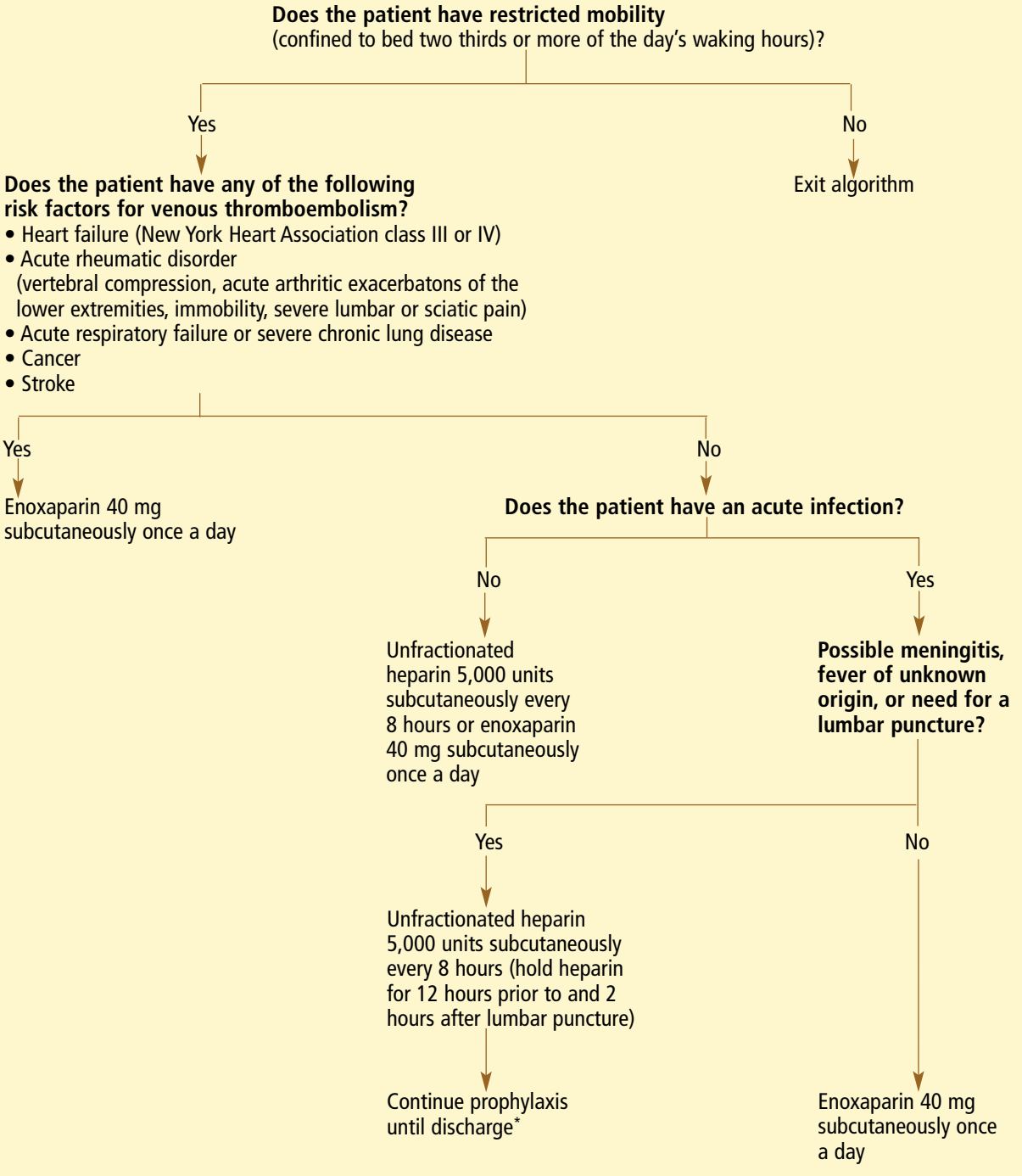
At 14 days, the incidence of VTE was 14.9% in the placebo group, 15.5% in the enoxaparin 20 mg group, and 5.5% in the enoxaparin 40 mg group ($P < .001$ vs placebo). The pattern was similar on long-term follow-up.[31,32] The lack of efficacy of enoxaparin 20 mg in this study could be explained by the 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]

**The ACCP strongly supports VTE prophylaxis and has issued guidelines**

### 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] Preprinted or computerized forms should be available. Such an approach has been successfully implemented at our institution (FIGURE 1).

## 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 hospital[41] 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 underestimated, 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.

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