

# Anticoagulant Prophylaxis in Medical Patients: An Objective Assessment

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Venous thromboembolism (VTE) is a clinically silent and potentially fatal disease that manifests as deep vein thrombosis (DVT) and pulmonary embolism. Venous thromboembolism remains a serious public health challenge, with an ever-increasing odds ratio of occurrence given the aging population in the United States. This article reviews the epidemiology of VTE; risk factor identification and stratification as a means of advancing awareness, prevention, and detection of VTE; and prophylaxis options and their outcomes, particularly administration of unfractionated heparin (UFH) 5000 U subcutaneously every 12 versus 8 hours in the at-risk medical patient population. The important studies comparing outcomes of these different UFH dosing regimens compared with placebo and low-molecular-weight heparins also are discussed. Consensus recommendations shaping contemporary clinical practice guidelines in this setting are highlighted. A systemwide approach to treatment of all medical patients who are risk stratified and receiving appropriate pharmacologic prophylaxis is recommended.

**Key Words:** unfractionated heparin, low-molecular-weight heparins, anticoagulant prophylaxis, venous thromboembolism, deep vein thrombosis, pulmonary embolism, VTE risk factors.

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality in the United States. Pulmonary embolism afflicts over 500,000 patients annually, causes 10% of all in-hospital deaths, and remains the single most important cause of maternal deaths associated with live births. Given that only one third of cases of proximal deep venous thrombosis (DVT) are clinically recognized, actual DVT rates may be as high as 2 million/year. It is estimated that 600,000 patients/year develop pulmonary embolism, and that 60,000 die of this complication.<sup>1–5</sup> Advanced age increases the risk

of developing VTE, with a probability of 10.7% by the age of 80 years. Unfortunately, autopsy studies continue to show that most cases of fatal pulmonary embolism are unrecognized and undiagnosed.<sup>6</sup>

A long-term morbid sequela of DVT is the recurring manifestation of postthrombotic syndrome, which is characterized by chronic pain, edema, or ulceration of the lower extremities. Postthrombotic syndrome develops in 30% of patients within 8 years of an initial venous thrombotic event, and its management is associated with high costs.<sup>7</sup>

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## VTE Risk Factors: Establish Need

Timely and appropriate prophylaxis is essential to minimize VTE events. Without prophylaxis, a DVT may occur in up to one of four hospitalized medical patients.<sup>7</sup> Numerous risk factors for VTE have been identified and are used to stratify both surgical and medical patients according to

their overall risk<sup>8</sup>:

- Increasing age (> 40 yrs)
- Prolonged immobility
- Stroke
- Paralysis
- Previous venous thromboembolism
- Cancer and its treatment
- Myocardial infarction
- Major surgery (especially involving the abdomen, pelvis, lower extremities)
- Trauma (particularly fractures of the pelvis, hip, leg)
- Congenitally acquired thrombophilic disorders (activated protein C resistance, antiphospholipid antibodies, protein C and S deficiency, antithrombin deficiency, dysfibrinogenemia)
- Severe infection
- Obesity
- Varicose veins
- Heart failure
- Indwelling central venous catheters
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy
- Estrogen therapy
- Chronic respiratory disease

Similar to major surgery, acute hospitalization for a medical condition poses a substantial risk of thromboembolic complications. Nearly all hospitalized medical patients have at least one VTE risk factor, and approximately 20% have three or more.<sup>9</sup> Two trials—Prophylaxis in Medical Patients with Enoxaparin (MEDENOX)<sup>10</sup> and Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT)<sup>11</sup>—further demonstrated that medical patients have an increased risk for VTE within our health care systems.

These trials compared the efficacy and safety of the low-molecular-weight heparins (LMWHs) enoxaparin (MEDENOX)<sup>10</sup> and dalteparin (PREVENT)<sup>11</sup> with placebo for prevention of VTE in acutely ill medical patients with recent immobility. In the placebo group of the MEDENOX trial, the frequency of VTE was 14.9% and proximal DVT 4.9%. These results clearly demonstrated that the medical patient population studied was at significant risk for a VTE event.

In a subgroup analysis of patients with New York Heart Association (NYHA) class III–IV heart failure and chronic heart failure, the frequency of VTE in those receiving placebo was 14.6% and

12.1%, respectively. In the PREVENT trial, the frequency of clinically important VTE in a moderately high-risk medical patient population was 5% in the placebo group. In addition, the results of both trials demonstrated that LMWHs significantly reduced the risk of VTE in medical patients compared with no prophylaxis.

The American College of Chest Physicians (ACCP) assigns its highest recommendation, 1A, for administration of either low-dose unfractionated heparin (UFH) or a LMWH in general medical patients with risk factors.<sup>12</sup> The rationale for prophylaxis is based on the high prevalence of VTE among hospitalized medical patients, the clinically silent nature of the disease, unreliable clinical diagnosis, associated morbidity and mortality, and the cost of treating a VTE event.

Prophylaxis continues to be underused in the at-risk medical patient population despite the known risks and the ACCP recommendation. A survey revealed that only 28% of medical inpatients with risk factors received VTE prophylaxis.<sup>13</sup> In addition, a large epidemiologic analysis of 5451 patients with confirmed DVT found that prophylaxis was omitted in 58% of the inpatients reviewed.<sup>14</sup> Underuse of VTE prophylaxis may result from clinicians' lack of awareness of the overall magnitude of this risk. Few VTE prophylaxis studies have been conducted in this heterogeneous medical patient population, and no one specialty has claimed responsibility. The ratio of surgical:medical patients who have been involved in VTE prophylaxis clinical trials is 100,000:10,000.<sup>9</sup> Finally, the tendency to focus only on the admission diagnosis during the hospital stay and not VTE prophylaxis may contribute to the problem.

#### VTE Risk Stratification: Whom to Target

An individual patient's underlying VTE risk factors appear to be as important as the acute clinical condition precipitating hospitalization and the need to be assessed through a thrombotic risk-benefit analysis.

Independent risk factors such as stroke, myocardial infarction, cancer, conditions requiring critical care, and spinal cord injury define the highest thromboembolic risk populations.<sup>8,9</sup> The moderate-risk groups, characterized by DVT rates of approximately 17%, represent patients with severe cardio-pulmonary diseases such as NYHA class III–IV

heart failure, pulmonary infection, or respiratory failure. Respiratory failure may result from community or nosocomial pneumonia, chronic obstructive lung disease, acute respiratory distress syndrome, pulmonary hypertension, or interstitial lung disease.<sup>10, 15, 16</sup>

Prolonged immobility or reduced mobility are two additional independent VTE risk factors that require consideration in assessing a patient's overall VTE risk. Immobility as a risk parameter is not meant to imply complete bed rest but functional impairment. In contemporary hospital medical practice, most patients have numerous risk factors for VTE. These risk factors are additive and need to be documented at hospital admission so that appropriate prophylaxis is begun in a timely manner.

Several institutions have adopted VTE risk assessment protocols to systematically identify and evaluate patients who require prophylaxis.<sup>17, 18</sup> To optimize outcomes, these assessment tools must incorporate clinical evidence in a manner that is simple to execute and is consistent across all patient populations. The challenge is to ensure that these recommendations become an integral component of daily practice for medical patients at risk.

### VTE Prophylaxis: Clinical Evidence

Venous thromboembolism prophylaxis in various patient populations is accomplished through the use of devices or pharmacologic agents or, in certain patients, a combination of both. Nonpharmacologic DVT prevention strategies are not recommended as a sole means of prophylaxis in medical patients at risk. Devices such as intermittent pneumatic compression, elastic stockings, and foot pumps have not undergone rigorous clinical trials and should be used cautiously. Due to this lack of clinical evidence, application of these devices is usually restricted to patients with a propensity for active bleeding. In terms of pharmacologic VTE prophylaxis for medical patients at risk, a few trials have assessed the efficacy and safety of low-dose UFH or LMWHs compared with placebo. In addition, limited head-to-head comparisons have been conducted.

Much of the information defining the role of UFH for VTE prophylaxis in medical patients has been extrapolated from data and experience gleaned from surgical patients. In an early attempt to evaluate UFH in medical patients, a randomized controlled trial investigated low-dose

UFH for prevention of fatal pulmonary embolism in patients with acute infectious diseases.<sup>19</sup> This study involved high-risk patients who clearly required effective VTE prophylaxis. Of 19,751 patients screened, 11,693 were determined eligible for the study.

Patients were randomized to receive either no prophylactic treatment (5917 control patients) or low-dose subcutaneous UFH 5000 U every 12 hours until hospital discharge or for a maximum of 3 weeks (5776 treatment patients). The follow-up period continued for 3 weeks after discharge or a maximum of 60 days from randomization. By intent-to-treat analysis, mortality was similar for the low-dose UFH treatment group and the control group (5.3% vs 5.6%, respectively,  $p=0.39$ .) Necropsy verified that pulmonary embolism occurred in 15 UFH-treated patients and 16 controls; no statistical difference was noted between subcutaneous UFH 5000 U every 12 hours and placebo. By a definition regarding the pharmacoeconomics of drug therapies for "cost-effectiveness,"<sup>20</sup> these results rendered the role of the every-12-hour UFH regimen for VTE prophylaxis as not cost-effective.

In contrast, another study demonstrated a mortality benefit in hospitalized medical patients treated with low-dose UFH every 12 hours compared with placebo.<sup>21</sup> However, potential selection bias, along with a significant reduction in the number of eligible patients in the treatment group, diminished the clinical applicability of these trial results.

Other studies also evaluated the efficacy and safety of low-dose UFH compared with placebo for VTE prophylaxis in patients with acute medical illnesses.<sup>22-24</sup> However, these trials are not recent and provide inconsistent results. In addition, efficacy end points were based on insensitive outcome markers and diagnostic testing. Other factors that limit application of earlier trial results to current practice are the sample size,<sup>23, 24</sup> selected patient populations,<sup>16</sup> absence of objective diagnostics,<sup>21</sup> and selected UFH regimens for study (subcutaneous UFH 5000 U twice/day).<sup>21, 24</sup>

Four clinical trials compared the efficacy and safety of low-dose UFH versus LMWH for VTE prophylaxis in medical patients at risk (Table 1).<sup>25-28</sup> Each trial used the same treatment regimen—subcutaneous enoxaparin 40 mg once/day versus subcutaneous UFH 5000 U 3 times/day.

The Prophylaxis in Internal Medicine with

**Table 1. Venous Thromboembolism Prophylaxis in Medical Patients in Various Trials**

Study Design, Patient Population	Treatment Regimen	Diagnostic Method	Frequency of VTE (%)	Results
MC, R, DB (n=959), medical illness, acute immobility, + additional risk factor, age $\geq$ 18 yrs <sup>25</sup>	Enoxaparin 40 mg s.c. q.d. vs Ca UFH 5000 U s.c. q8h x 7 days	Duplex B-mode scan or duplex ultrasound-venography confirmation	LMWH: 0.2 Low-dose UFH: 1.4	Equivalence
MC, R (n=665), NYHA class III-IV CHF or respiratory disease <sup>26</sup>	Enoxaparin 40 mg s.c. q.d. vs Ca UFH 5000 U s.c. q8h x 8-12 days	D-dimer assay, fibrin monomer-venography confirmation	LMWH: 8.4 Low-dose UFH: 10.4	Equivalence
R (n=877), severe respiratory disease, NYHA class III-IV CHF, or acute ischemic stroke <sup>27</sup>	Enoxaparin 40 mg s.c. q.d. vs UFH 5000 U s.c. q8h	Venography	VTE + death: LMWH: 15.6 Low-dose UFH: 22.1	p=0.04, relative risk reduction 29%
MC, R, DB (n=212), ischemic stroke with acute onset of paralysis <sup>28</sup>	Enoxaparin 40 mg s.c. q.d. vs UFH 5000 U s.c. q8h x 8-12 days	Venography	LMWH: 19.7 Low-dose UFH: 34.7	Equivalence
MC, R, DB (n=442), acute medical illness, acute bed rest, unable to ambulate 10 m unassisted, age $\geq$ 65 yrs <sup>29</sup>	Enoxaparin 20 mg s.c. q.d. vs Ca UFH 5000 U s.c. q12h x 10 days	<sup>125</sup> I-fibrinogen uptake test	LMWH: 4.8 Low-dose UFH: 4.6	Equivalence

MC = multicenter; R = randomized; DB = double-blind; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism; Ca = calcium; CHF = chronic heart failure; NYHA = New York Heart Association.

Adapted with permission from reference 8.

Enoxaparin (PRIME) trial assessed the efficacy and safety profile of low-dose UFH versus enoxaparin for DVT prophylaxis in 959 medical patients.<sup>25</sup> This multicenter, double-blind, equivalence study randomized an unselected or diverse group of medical patients expected to be immobilized for more than half of the day during the 7-day study period. These patients also had at least one additional VTE risk factor (age > 60, malignancy, obesity, previous VTE event, heart failure, paresis, hemiplegia, or severe infection).

New VTE disease developed in 0.2% of the enoxaparin group and 1.4% of the heparin group (p=NS). The safety analysis found fewer adverse events and major hemorrhagic complications in the enoxaparin group. These results indicate that subcutaneous enoxaparin 40 mg once/day is at least as effective as subcutaneous UFH 5000 U 3 times/day for VTE prophylaxis of immobilized medical patients and is associated with fewer adverse events.

The Prevention in Cardiopulmonary Disease

with Enoxaparin (PRINCE) study involved 64 centers and evaluated patients with severe respiratory disease and NYHA class III-IV heart failure.<sup>26</sup> A total of 665 patients were randomized to either enoxaparin daily or low-dose UFH every 8 hours for approximately 10 days. The efficacy outcome of this trial was statistically significant, favoring LMWH as demonstrated by DVT rates of 7.9% and 9.9% for enoxaparin and UFH, respectively.

In a subgroup analysis, patients with heart failure had a higher frequency of VTE than those with respiratory failure. Among the patients with heart failure, enoxaparin demonstrated a significant reduction in VTE compared with low-dose UFH (DVT rates 9.7% vs 16.1%, respectively). However, there was no significant difference between treatments in the respiratory disease subgroup. With respect to major hemorrhage for the study overall, the frequency was low and comparable between groups. However, hematomas at the injection site were more common in

patients receiving low-dose UFH versus enoxaparin (12.6% vs 7.2%, respectively).

Based on the overall efficacy results of the PRINCE study, subcutaneous enoxaparin 40 mg once/day was at least as safe and effective as subcutaneous low-dose UFH 3 times/day for VTE prevention in patients with severe cardiopulmonary disease.

One study evaluated the efficacy of subcutaneous UFH 5000 U 3 times/day versus daily enoxaparin in a randomized trial of 877 high-risk medical patients diagnosed with severe respiratory disease, NYHA class III–IV heart failure, or acute ischemic stroke.<sup>27</sup> Thromboembolic events and death occurred in 15.6% of the patients randomized to LMWH versus 22.1% of those receiving low-dose UFH, indicating superiority of enoxaparin ( $p=0.04$ ). The benefit associated with LMWH therapy increased with the overall increasing risk of VTE. A statistically significant advantage favored the LMWH over UFH for adverse events (9.1% vs 19.6%, respectively,  $p=0.001$ ).

Another study evaluated VTE prophylaxis regimens in 212 patients who had recently experienced an ischemic stroke with onset of paralysis.<sup>28</sup> The frequency of VTE with daily enoxaparin versus low-dose UFH 3 times/day was 19.7% versus 34.7%, respectively ( $p=0.044$ ). Safety profiles were comparable between groups.

Administration of LMWH in medical patients also has been compared with low-dose UFH twice/day for VTE prevention. One trial found that a lower daily dose of enoxaparin 20 mg was comparable to subcutaneous UFH 5000 U every 12 hours in an unselected group of elderly medical inpatients with limited mobility (Table 1).<sup>29</sup> Considering that the efficacy of subcutaneous enoxaparin 20 mg/day in moderately ill medical patients was comparable to that of placebo in the MEDENOX trial,<sup>10</sup> the results of this study raised questions regarding the true benefit of UFH every 12 hours in medical patients at risk.

In summary, based on randomized placebo and head-to-head trials, low-dose UFH every 8 hours is recommended over the every-12-hour regimen for VTE prophylaxis in medical patients at risk. A review of the literature did not produce sound studies supporting twice-daily low-dose UFH in this patient population. In fact, two studies evaluating mortality in medical patients who received either subcutaneous UFH 5000 U twice/day or no prophylaxis yielded conflicting results.<sup>19, 21</sup>

The overall use of low-dose UFH does not compare favorably with LMWHs in this population. A meta-analysis of VTE prophylaxis trials in medical patients suggests trends toward lower rates of DVT (relative risk [RR] 0.83, 95% confidence interval [CI] 0.56–1.24) and pulmonary embolism (RR 0.74, 95% CI 0.29–1.88), and significant reduction in major bleeding (RR 0.48, 95% CI 0.23–1.00) with administration of LMWHs versus low-dose UFH.<sup>9</sup>

### VTE Prophylaxis: Practice Guidelines

Although clinical evidence supports the use of low-dose UFH every 8 rather than 12 hours, this conclusion is operationally problematic. The standard of care in the United States has been to administer UFH 5000 U every 12 hours. Dosing 3 times/day is more labor intensive, is associated with poor compliance, and is actually less likely to occur outside of a rigorously controlled clinical trial. Thus, integrating this regimen into clinical practice through established guidelines is associated with a multitude of barriers.

Efforts to establish low-dose UFH as the primary agent for VTE prophylaxis in hospitalized medical patients to minimize costs have been described.<sup>30</sup> A pharmacy-conducted automatic substitution program targeted eligible medical patients receiving enoxaparin prophylaxis once or twice/day for conversion to a regimen of low-dose UFH 3 times/day. Unfortunately, when the authors reported the accepted recommendations for 59 (67%) of the 88 patients involved, they failed to differentiate between the new twice/day versus 3 times/day UFH physician orders.

This information would have provided true program acceptance rates. In addition, the authors indicated that enoxaparin was prescribed twice/day for this patient population at their facility. Based on results from the MEDENOX trial,<sup>10</sup> it may have been more appropriate for the authors to channel cost-reduction efforts toward ensuring a safe and effective daily dosing with an LMWH rather than attempt to suggest a UFH regimen associated with poor compliance and an increased risk of major bleeding.<sup>9</sup> Also, a 33% rejection rate by treating physicians may well portend the overall acceptance of such a conversion program.

A report evaluating current practice studied failed prophylaxis regimens compared with no prophylaxis in 384 hospital patients with new-onset VTE (Figure 1).<sup>31</sup> Of the 201 patients whose VTE prophylaxis was unsuccessful, 112

(56%) had received an anticoagulant. Of these patients, 61% were administered UFH as monotherapy, which represented the highest prophylaxis failure rate of all other regimens, such as warfarin alone (29%) and an LMWH alone (< 3%).

Pulmonary embolus was a major contributor to death in 13 patients. The VTE prophylaxis failed in 12 patients, five of whom were treated with UFH monotherapy, four with UFH in combination with mechanical interventions, one with warfarin monotherapy, one with a warfarin-UFH combination, and one with an LMWH-UFH combination. These data play an important role in tempering enthusiasm for VTE prevention guidelines recommending low-dose UFH as the primary agent for prophylaxis in the medical patient population.

In summary, practice guidelines to assist health care providers are necessary when addressing the clinical challenges posed by medically ill, immobile patients who are admitted in our health care systems. Data that have supported clinical, if not economic, decisions to choose UFH 5000 U twice/day are dated and methodologically flawed. If subcutaneous UFH 5000 U 3 times/day is recommended for these patients in an institution, clinicians need to be aware of the caveats cited regarding its successful use and the potential for therapeutic misadventure. Alternatives available today are equivalent, if not superior, to low-dose UFH. Sound clinical evidence supports the

benefit these agents provide for medical patients at risk of VTE.

## Conclusion

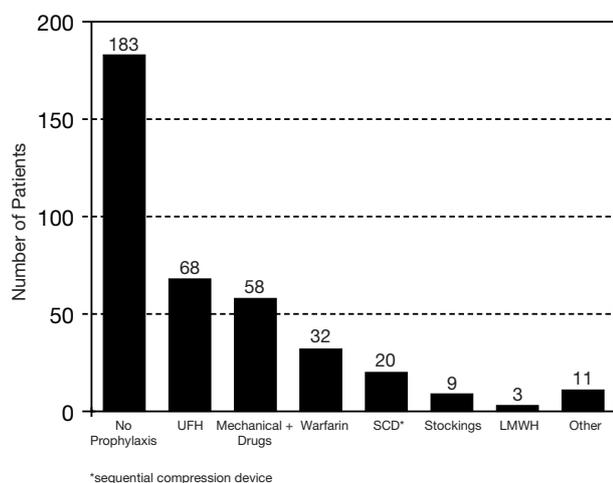
Underuse of VTE prophylaxis is a health care crisis. Only about one fourth of medical inpatients with risk factors receive this treatment. Barriers preventing the start of appropriate therapy are the failure to evaluate patients in a systematic and timely manner, inconsistencies in the literature regarding optimal VTE prophylaxis regimens, concerns related to potential bleeding complications, and cost. The VTE risk-stratification tools can be implemented successfully to improve clinical outcomes in terms of patient identification and the start of optimal prophylaxis.

The ACCP has assigned its highest recommendation, 1A, for administration of either low-dose UFH or LMWH in general medical patients with risk factors. However, these recommendations list agents in a general format or by class. Thus, clinicians must refer to the available clinical evidence to identify optimal regimens. Efficacy studies in this patient population have identified LMWHs as either equivalent or superior to low-dose subcutaneous UFH 5000 U every 8 hours. A trend toward an overall improved safety profile is seen with the LMWHs versus UFH for this indication.

In most health care institutions, UFH most frequently is given every 12 hours for VTE prophylaxis in medical patients at risk. The few studies evaluating the use of this regimen were small and yielded conflicting results. Approaches to drug cost reduction that focus on the control of LMWH use and the substitution of UFH for VTE prophylaxis must be thoroughly assessed and balanced against the potential increase of VTE and the costs associated with its management.

In terms of drug acquisition costs, low-dose UFH is clearly less expensive than any LMWH. However, LMWHs are effective and safe for VTE prevention in medical patients at risk, possess a favorable pharmacokinetic and adverse-event profile, and are more convenient and less labor intensive in terms of administration. Institutions endorsing UFH rather than an LMWH for VTE prophylaxis in this patient population should consider all the clinical and economic ramifications of such a decision.

Recommendations of the Heparin Consensus Group for VTE prophylaxis in medical patients at risk are provided in Appendix 1.



**Figure 1.** Retrospective review of 384 patients who developed VTE during a hospital stay or within 30 days of discharge. UFH = unfractionated heparin; SCD = sequential compression device; LMWH = low-molecular-weight heparin. (Adapted from reference 31.)

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**Appendix 1. Recommendations for VTE Prophylaxis in Medical Patients at Risk**


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1. All medical patients should be stratified according to risk of VTE.
  2. Medical patients at risk for a VTE event should receive appropriate pharmacologic prophylaxis.
  3. Low-dose UFH every 8 hours or a LMWH is recommended for VTE prophylaxis in medical patients at risk. Although the acquisition cost of UFH is low, LMWHs offer a convenient and safe advantage.
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