THROMBOPHYLAXIS IN MEDICAL PATIENTS: LESSONS FROM MEDENOX

Russell D. Hull, MBBS, MSc

ABSTRACT

The use of thromboprophylaxis has been less studied in general medical patients than in surgical patients. A need for additional medical evidence in this area led to the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial. This trial was designed to assess the risk of venous thromboembolism (VTE) in moderate-risk medical patients and to evaluate the efficacy and safety of 2 regimens of low-molecular-weight heparin (LMWH) for the prevention of deep vein thrombosis and pulmonary embolism. The study found that 40 mg enoxaparin QD was both safe and efficacious in reducing the incidence of VTE. Moreover, a meta-analysis of randomized trials comparing the safety and efficacy of LMWH with low-dose unfractionated heparin (UFH) in internal medicine found that LMWH and UFH have similar efficacy. However, LMWH may be associated with a significantly lower risk of major bleeding as compared with UFH. These findings offer sufficient evidence to support the need for thromboprophylaxis in medical patients. Current recommendations from the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy are for the use of thromboprophylaxis in medical patients at moderate or high risk of VTE.

Despite the high incidence of deep vein thrombosis (DVT) in general medical patients, the use of thromboprophylaxis has been less studied in this group than in surgical patients. Although studies have shown that patients who have undergone hip replacement and knee replacement—as well as other patients who have experienced surgical and trauma events—are at high risk for DVT, existing and emergent medical evidence shows some surprising results: medical patients are also at high risk for DVT. The medical literature suggests that in the absence of thromboprophylaxis, the incidence of DVT is 19% in medical patients, excluding cases of ischemic stroke and acute myocardial infarction. These significant findings provide a mandate for clinicians to reconsider the classification of nonsurgical patients and abandon the traditional classifications of low, moderate, and high risk. Medical patients today are in the high-risk group, a status that reflects the change in the hospitalization and the acuities of these patients.

Combining anticoagulant (low-molecular-weight heparin [LMWH], unfractionated heparin [UFH], warfarin) and mechanical (elastic stockings, intermittent pneumatic compression) prophylactic methods has been shown to reduce the incidence of venous thromboembolism (VTE), as shown in Table 1. The medical evidence suggests that warfarin is of little value in medical patients, with the exception of very high-risk patients in whom other prophylaxis measures are ineffective. While multiple prophylactic therapies are available, recent medical trials suggest that the selection of therapy in specific medical patient populations is an important clinical decision.

For patients with acute myocardial infarction (MI), the Grade 1A recommendation is the administration
of prophylactic or therapeutic anticoagulant therapy with subcutaneous low-dose unfractionated heparin (LDUH) or IV heparin. In patients with acute MI, an overlap clearly exists between the thrombotic process and the artery and the need for preventing venous thrombosis in the limb.

For patients with ischemic stroke, the risk of cerebral hematoma or a bleed into an infarct is of concern. For patients with ischemic stroke and impaired mobility, routine use of LDUH, LMWH, or the heparinoid known as danaparoid are Grade 1A recommendations. If anticoagulant prophylaxis is contraindicated, mechanical prophylaxis such as elastic stockings or intermittent pneumatic compression is recommended (Grade 1C+). The 1C+ recommendation is based on the fact that although elastic stockings and intermittent pneumatic compression were found to be protective in other patient populations, there is a lack of direct data applying such findings to patients with ischemic stroke.

For other medical conditions, LDUH or LMWH are Grade 1A recommendations for general medical patients with risk factors for VTE (including cancer, bed rest, heart failure, and severe lung disease). For LMWH, either a moderate-risk dose or a high-risk dose is suggested. However, there is compelling new medical evidence, not yet incorporated into the recommendation, that suggests a high-risk LMWH dosing regimen is entirely appropriate for this population. This data is presented in the following paragraphs.

In an epidemiologic analysis, Samama identified the following intrinsic risk factors for DVT in medical outpatients:

- History of DVT or pulmonary embolism (PE)
- Venous insufficiency
- Chronic heart failure
- Obesity (body mass index >30 kg/m²)
- Standing position for more than 6 hours per day
- History of more than 3 pregnancies.

Triggering factors for DVT identified by the author included the following:

- Pregnancy
- Violent effort or muscular trauma
- Deterioration in general condition
- Immobilization (total confinement to bed or to bed and armchair)
- Long-distance travel
- Infectious disease.

The author concluded there is a higher risk of DVT in patients presenting with more than 1 risk factor.

### Severe Pulmonary Embolism Associated with Air Travel

Air travel is believed to be a risk factor for pulmonary embolism (PE), but the relation between PE and distance flown by the patient was only recently documented. A study by Lapostolle et al investigated the relationship between the duration of air travel and the patient's risk for PE. In an observational analysis, the investigators reviewed all cases of patients with PE who required medical care upon arrival at a busy international airport. Of the 135.3 million passengers arriving at an international airport during the study period, 56 passengers had confirmed PE. The incidence of PE significantly increased in passengers traveling 3100 miles or more to 1.5 cases per million passengers. For those traveling 6200 miles or more the incidence of PE was 4.8 cases per 1 million passengers. These findings suggest that a greater distance traveled is a significant contributing risk factor for PE.

A recent randomized trial assessed the frequency of DVT in long-haul, economy-class airline passengers.

### Table 1. Recommended DVT Prophylaxis

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip replacement</td>
<td>WAR, LMWH H</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>WAR, LMWH H, IPC</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>WAR, LMWH H</td>
</tr>
<tr>
<td>Major trauma</td>
<td>LMWH H, IPC</td>
</tr>
<tr>
<td>Abdominal/pelvic cancer surgery</td>
<td>LMWH H, IPC, W AR</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>UFH, LMWH H, IPC, W AR, ES</td>
</tr>
<tr>
<td>Medical patients ≥ 40 yrs with immobilization</td>
<td>UFH, ES, LMWH H</td>
</tr>
</tbody>
</table>

LMWH H = low-molecular-weight heparin; ES = elastic stockings; IPC = intermittent pneumatic compression; UFH = unfractionated heparin; WAR = warfarin.

Adapted with permission from reference 6.
and the efficacy of graduated-elastic compression stockings in the prevention of DVT. This trial showed that symptomless DVT occurs in approximately 10% of long-haul airline travelers. None of the patients who wore Class I elastic compression stockings developed DVT. Superficial thrombophlebitis developed in 4 passengers who were wearing compression stockings (Table 2). These findings suggest that elastic compression stockings reduce the risk of symptomless DVT after air travel.

Very recent data from the LONFLIT studies evaluated the incidence of DVT associated with air travel in high-risk patients. After average flight duration of 12.4 hours, the incidence of DVT in high-risk patients was 2.7%. The LONFLIT3 study evaluated 2 methods of DVT prevention in high-risk subjects: aspirin (400 mg once daily for 3 days, starting 12 hours prior to air travel) and LMWH (1 dose of enoxaparin injected 2 to 4 hours prior to air travel). Of the 82 subjects in the control group, 4 (4.8%) had DVT and 2 had superficial thromboses. In total, a thrombotic event was diagnosed in 4.8% of limbs. Of 84 subjects in the aspirin-treatment group, 3 (3.6%) patients had DVT and 2 had superficial thromboses. In total, a thrombotic event was diagnosed in 3.6% of limbs. In the LMWH group (82 subjects), there were no cases of DVT; one case of superficial thrombosis was documented. In total, a thrombotic event was diagnosed in 0.6% of limbs (P<0.002 in comparison with the other 2 groups). The use of LMWH—although it was off-label—was more successful than the use of aspirin in preventing thrombotic events and does raise hope for a successful intervention, particularly for use in very high-risk patients. The investigators suggest that 1 dose of LMWH is an important option to consider in high-risk subjects during long-haul flights.

**DVT Risk in Medical Patients**

The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial evaluated the efficacy of 2 dosage regimens of LMWH (enoxaparin) for prevention of VTE in acutely ill medical patients. MEDENOX, a prospective, double-blind, randomized, placebo-controlled trial, showed that symptomless DVT occurs in approximately 10% of long-haul airline travelers. None of the patients who wore Class I elastic compression stockings developed DVT. Superficial thrombophlebitis developed in 4 passengers who were wearing compression stockings (Table 2). These findings suggest that elastic compression stockings reduce the risk of symptomless DVT after air travel.

### Table 2. Frequency and Prevention of Symptomless DVT in Long-Haul Flights

<table>
<thead>
<tr>
<th>Characteristics of Study Groups</th>
<th>No Stockings</th>
<th>Stockings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>116</td>
<td>115</td>
</tr>
<tr>
<td>Age in years (median, IQR)</td>
<td>62 (56–68)</td>
<td>61 (56–66)</td>
</tr>
<tr>
<td>Number of women</td>
<td>61 (53%)</td>
<td>81 (70%)</td>
</tr>
<tr>
<td>Number with varicose veins</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Days of stay (median, IQR)</td>
<td>17 (13–32)</td>
<td>16 (13–27)</td>
</tr>
<tr>
<td>Hours flying time (median, IQR)</td>
<td>22 (18–36)</td>
<td>24 (19–35)</td>
</tr>
<tr>
<td>Hemoglobin (g/L) (median, IQR)</td>
<td>142 (133–149)</td>
<td>140 (133–147)</td>
</tr>
<tr>
<td>WBC (x10^9/L) (median, IQR)</td>
<td>5.9 (5.0–7.3)</td>
<td>6.0 (5.0–6.9)</td>
</tr>
<tr>
<td>Packed cell volume (median, IQR)</td>
<td>0.44 (0.42–0.47)</td>
<td>0.44 (0.41–0.46)</td>
</tr>
<tr>
<td>Platelets (x10^9/L) (median, IQR)</td>
<td>240 (206–272)</td>
<td>242 (219–290)</td>
</tr>
<tr>
<td>Number FVL positive</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Number PGM positive</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Median (interquartile range) shown, unless otherwise indicated. WBC = white blood cells; FVL = factor V Leiden; PGM = prothrombin gene mutation. Adapted with permission from reference 9.
trial, enrolled 1102 hospitalized patients who were randomized to receive 40 mg of enoxaparin, or 20 mg of enoxaparin, or a placebo, which was given subcutaneously once daily for 6 days to 14 days. The patients were randomly assigned to treatment groups if they had congestive heart failure, acute respiratory failure, or 1 of several specified medical conditions that had to be associated with at least 1 additional predefined VTE risk factor. Among the study participants, 53.5% were hospitalized with respiratory failure; 53.1% with infectious disease; 34.2% with heart disease; 9.1% with rheumatic disease; and 0.5% with bowel disease. The primary outcome was DVT by venography or symptomatic PE between day 1 and day 14. After 14 days, the incidence of VTE was 5.5% in the group receiving 40 mg of enoxaparin and 14.9% in the placebo group—a significantly lower incidence with a relative risk reduction of 63%. The incidence of detected thromboembolism in the group receiving 20 mg enoxaparin was similar to that of the placebo group. Although physicians may have predicted that the 20-mg dose of enoxaparin was most appropriate for such patients, these current data provide good medical evidence that the understanding of efficacy in medical patients must be upgraded. The incidence of adverse effects did not significantly differ between the placebo group and either of the enoxaparin groups.

Efficacy persisted throughout 110 days of follow-up, raising the question as to whether it might be appropriate to continue drug therapy for longer periods of time following hospital discharge, as hospital stays have been greatly shortened in recent years. These findings suggest that further clinical trials should be performed evaluating out-of-hospital long-term prophylaxis in medical patients.

A Kaplan-Meier estimate of the probability of survival (Figure) demonstrates that survival rates were higher in patients who received the 40-mg dose of LMWH, survival rates were equal in the groups receiving 20 mg LMWH and placebo. Investigators are currently recruiting 6000 patients for an international study to determine the efficacy of continuing prophylaxis 28 days following hospital discharge of patients with VTE.

Although meta-analyses findings should be reviewed with some caution (as they tend to be hypothesis-forming), findings of a meta-analysis of smaller trials in medical patients suggest that LMWH is associated with a 52% reduction in major hemorrhage, as compared with UFH (P = .049). However, this reduction in major bleeding was almost completely from only 3 of the 9 studies reviewed. While the reduction in major bleeding in LMWH vs. LDUH noted in this meta-analysis is a potentially important finding, it must be confirmed by additional clinical study.

**Conclusion**

Findings from the studies reviewed here offer sufficient evidence to support the need for thromboprophylaxis in medical patients. Current recommendations of the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy are to use thromboprophylaxis in medical patients at moderate or high risk of VTE. It is anticipated that data from the MEDENOX study will be incorporated into future consensus guidelines on the prevention of VTE. Further studies are required to assess the benefit-to-risk ratio of therapy in other clearly defined medical groups.

**REFERENCES**