

## **Venous Thromboembolism in Medically Ill Patients—Identifying Risk and Strategies for Prevention**

### **Introduction**

Venous thromboembolism (VTE) is a condition that has multiple causes but few warning signs. Consequently, pulmonary embolism (PE) and deep vein thrombosis (DVT), the two components of VTE, often go unpredicted. This is especially true for medical patients, in which thromboembolic risk has been less clearly established than for surgical patients.

Several factors are thought to be associated with an increased risk of VTE, including extended periods of immobility, advancing age, major surgery, prior VTE, and chronic heart failure (Anderson, 2003). Strong risk factors for VTE include hip or knee replacement and major general surgery, whereas weaker risk factors include increasing age and laparoscopic surgery. Given the wide range of risk associated with various factors, the decision to provide VTE prophylaxis should take into account the specific risk of each patient (Anderson, 2003); however, guidelines indicate that most hospitalized patients should receive prophylaxis for VTE. This report will discuss these guidelines, the high prevalence of VTE among medical patients, and clinical studies of thromboprophylaxis in medical ill patients.

### **Prevalence of VTE Among Medical Patients**

In a typical hospital population, 78% of patients have one or more risk factors for VTE, and approximately 20% of patients have at least 3 risk factors (Anderson, 1992). Overall, the incidence of VTE among medically ill patients is estimated to be about 18 to 23% (Gerotziafaz, 2004).

The benefits of treating and preventing VTE in surgical patients are well established; however, many at-risk hospitalized medical patients do not appear to be receiving adequate prophylaxis. In 1995, Hirsch and colleagues reported that the rate of DVT was unexpectedly high in medical ICU patients, despite the fact that prophylaxis was administered in 61% of the patients (Hirsch, 1995). DVT was detected with ultrasound in one third of 100 eligible patients over an 8-month period. About half of the cases involved proximal lower extremity DVT. Furthermore, no difference in risk factors, including age, gender, body mass index, diagnosis of cancer, recent surgery, duration of hospitalization prior to DVT detection was observed among those that developed DVT and those that did not. Thus, the authors concluded that intensive prophylaxis regimens are warranted in this patient population.

### **Current ACCP Recommendations**

Pharmacologic approaches currently indicated for thromboprophylaxis include unfractionated heparin (UFH); low-molecular-weight heparin (LMWH) (enoxaparin and dalteparin); fondaparinux, a novel antithrombotic agent specific for factor Xa; and vitamin K antagonists (VKA), such as warfarin. The Seventh ACCP Conference on

Antithrombotic and Thrombolytic Therapy recently updated evidence-based guidelines for the prevention of VTE (Geerts, 2004). The new guidelines include stronger evidence-based recommendations for the use of VTE prophylaxis in various settings compared with previous guidelines (Geerts, 2001).

Notably, the new guidelines state that “all institutions should have a program in place that allows for the evaluation of a patient’s risk of developing VTE. If patients are found to be at risk of VTE, appropriate prophylaxis should be implemented.” They also suggest that all patients admitted to the intensive care unit should be assessed for their risk of VTE, and most should receive thromboprophylaxis. In addition, all patients with at least one risk factor for VTE who have undergone trauma or who are confined to bed should receive thromboprophylaxis, as should acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease (Geerts, 2004).

For surgical patients, low-dose UFH or LMWH should be used for moderate- and higher-risk patients, with dosing being dependent on level of risk. In addition, thromboprophylaxis should be used in all patients undergoing major gynecologic surgery or major, open urologic procedures. In patients undergoing hip or knee replacement surgery, LMWH, fondaparinux, or adjusted-dose vitamin K antagonist (VKA) should be used for at least 10 days. For patients undergoing hip fracture surgery, low-dose UFH in addition to LMWH, fondaparinux, or VKA is recommended (Geerts, 2004).

### **Use of Antithrombotic Therapy—Guidelines Versus Reality**

A recent report suggests that thromboprophylaxis is significantly underused in US hospitals (Tapson, 2005). According to the researchers, a large proportion of hospitalized patients do not receive adequate antithrombotic therapy for prevention of thromboembolic disease. In their study, Tapson and colleagues randomly selected data from 3778 inpatient medical records at 38 US hospitals. Patients were undergoing treatment for atrial fibrillation, acute myocardial infarction, DVT, or PE. The study also included patients receiving thromboprophylaxis for total hip or knee replacement, or hip fracture surgery. Among patients with atrial fibrillation at high risk for stroke, just over half (54.7%) received warfarin, but about 20% received neither aspirin nor warfarin. Among patients with acute myocardial infarction, about one fourth did not receive aspirin when they arrived at the hospital. For orthopedic surgery procedures, about 85% of patients received prophylaxis with warfarin or a parenteral anticoagulant agent. In about half of patients with PE and/or DVT, prophylaxis was discontinued before an international normalized ratio (INR) of  $\geq 2.0$  or greater was achieved for  $\geq 2$  days. Moreover, patients with VTE rarely received bridge therapy (an injectable anticoagulant agent plus warfarin) when leaving the hospital, despite the fact that the length of time to discharge was longer when patients received warfarin alone (4.0 versus 8.1 days;  $P < .001$ ) (Tapson, 2005). Thus, antithrombotic use appears to vary depending on medical condition and is underused in some patients.

In their report, Arnold and colleagues reported that 17.4% of 253 objectively diagnosed

cases could have been prevented had thromboprophylaxis guidelines had been followed (Arnold, 2001). Among the preventable cases, the most frequent reasons for insufficient prophylaxis were omission of prophylaxis (47.7%), inadequate duration of prophylaxis (22.7%), and incorrect type of prophylaxis (20.5%). Common surgical and medical indications for thromboprophylaxis among the preventable cases included admission to hospital for pneumonia, nonorthopedic surgery, and stroke with lower limb paralysis; common risk factors for VTE included obesity, recent immobility, and malignancy.

In an epidemiological study that included 5,451 patients with ultrasound-confirmed DVT, 2726 patients had their DVT diagnosed while in the hospital. Of those, only 42% received prophylaxis within 30 days before diagnosis (Goldhaber, 2004). The five most frequent co-morbidities among these patients were hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), cancer (32%), and obesity (27%). Among the 2872 nonsurgical patients, the rate of prior prophylaxis was only 20% compared with 43% of the 2094 surgical patients. Thus, the results of this large study also indicate that thromboprophylaxis is considerably underused, especially among medical patients.

### **Strategies for Preventing VTE in Medical Patients**

Evidence of the benefits of thromboprophylaxis in medical patients has been derived from smaller randomized trials that took place before the introduction of newer, more effective therapies. Consequently, the effects of medical patients are less clear than they are for surgical patients (Gallus, 1998). Various studies are beginning to confirm the benefits of thromboprophylaxis specifically in the medical patient population. These include the Medenox trial, the Prime study, the Prince study, the Prevent study, and the Artemis trial. Collectively, the findings suggest that LMWH (enoxaparin 40 mg or dalteparin 5000 IU subcutaneously once daily for 10 days) as well as fondaparinux 2.5 mg subcutaneously once daily for 10 days demonstrate a favorable risk-benefit ratio in the prevention of venous thromboembolism in acutely ill medical patients (Gerotziafas, 2004).

In the landmark Medenox trial, two doses of enoxaparin (20 mg and 40 mg once/day) were compared with placebo in medical patients (Samama, 1999). Prophylactic treatment with 40 mg per day of enoxaparin given subcutaneously was found to significantly reduce the risk of VTE compared with placebo (5.5% for enoxaparin versus 14.9% for placebo; relative risk, 0.37; 97.6% confidence interval [CI], 0.22 to 0.63;  $P < .001$ ). In addition, the incidence of VTE at Day 14 was significantly lower for patients receiving enoxaparin 40 mg compared with placebo ( $P = .0002$  for all VTE, and  $P = .0370$  for proximal DVT), and this benefit was maintained at 3 months. A subsequent analysis of data from the Medenox trial also indicated that risk of VTE was increased in patients with acute infectious disease, cancer, age  $> 75$  years, and a history of VTE (Alikhan, 2004).

The Prevent study compared dalteparin with placebo in the prevention of VTE in 3706 medical patients. Patients were randomly assigned to receive either subcutaneous

dalteparin 5000 IU daily or placebo for 14 days (Leizorovicz, 2004). The incidence of VTE was 4.96% in the placebo group versus 2.77% in the dalteparin group, for a relative risk reduction of 45% ( $P = .0015$ ). Likewise, the ARTEMIS trial compared fondaparinux with placebo in acutely ill elderly medical patients and found the incidence of VTE at Day 15 to be 10.5% in the placebo group versus 5.6% in the fondaparinux group (relative risk reduction, 49.5%;  $P = .0029$ ) (Cohen 2003).

Enoxaparin has also been compared in head-to-head trials with UFH. The Prime study, a randomized, double-blind controlled trial comparing enoxaparin 40 mg/day with UFH in a high-risk group of 959 hospitalized medical patients, found that enoxaparin was comparable to UFH in preventing VTE, with fewer adverse events (Lechler, 1996). Similarly, the Prince study compared the efficacy and safety of 10 days of enoxaparin (40 mg/day subcutaneously) versus UFH (5000 IU three times/day subcutaneously) in 665 medical patients with severe cardiopulmonary disease (Kleber, 1998). As with the Prime study, the results indicated that enoxaparin was as effective as UFH 5000 IU given 3 times/day.

Enoxaparin has also been found to be superior to UFH in medical patients at increased-to-high risk of VTE (Harenberg, 1999). Harenberg and colleagues analyzed data from patients with severe respiratory disease, severe heart failure, or acute ischemic stroke. A total of 877 patients received either 40 mg enoxaparin once a day or 5000 IU UFH three times a day. Among the 630 patients eligible for the efficacy analysis, thromboembolic events with subsequent death occurred in 15.6% of the patients in the enoxaparin group compared with 22.1% in the UFH group. Risk of VTE was highest among patients with acute ischemic stroke, followed by patients with severe heart failure and severe respiratory disease. Bleeding events occurred in 1.8% of the enoxaparin group versus 3.2% in the UFH group.

Finally, the ongoing EXCLAIM study will help clarify the benefits of extended prophylaxis among medical patients. This study is evaluating the role of extended prophylaxis with enoxaparin among approximately 5800 medical patients. Patients will receive enoxaparin 40 mg subcutaneously once/day versus placebo for 28 days after 10 days of enoxaparin. The endpoints will include the incidence of ultrasound-confirmed VTE, major bleeding, and mortality.

### **Conclusion**

Clearly, VTE prophylaxis continues to be underutilized in medically ill patients. These patients are at significant risk of VTE and require prophylaxis, an objective that is supported by the recent ACCP guidelines. In addition, several lines of clinical evidence support the use of prophylaxis in this subgroup of patients. Improved systems are needed in medically ill patients to help improve outcomes and compliance for the use of VTE prophylaxis.

### **References**

Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism.

*Circulation*. 2003;107:19-16.

Gerotziafas GT, Samama MM. Prophylaxis of venous thromboembolism in medical patients. *Curr Opin Pulm Med*. 2004;10:356-365.

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.

Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA*. 1995;274:335-337.

Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:338S-400S.

Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest*. 2001;119:132S-175S.

Tapson VF, Hyers TM, Waldo AL, et al. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. *Arch Intern Med*. 2005;165:1458-1464.

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.

Goldhaber SZ, Tapson VF; DVT FREE Steering Committee. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol*. 2004;93:259-262.

Gallus AS, Nurmohammed M, Kearon C, Prins M. Thromboprophylaxis in non-surgical patients: who, when and how? *Haemostasis*. 1998;28 Suppl 3:71-82.

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.

Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med*. 2004;164:963-968.

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;110:874-879.

Cohen AT, Davidson BL, Gallus AS et al. Fondaparinux for the prevention of VTE in acutely ill medical patients. *Blood* 2003; 102: 42 (abstract).

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.

Kleber FX, Witt C, Flosbach CW, et al. Study to compare the efficacy and safety of the LMWH enoxaparin and standard heparin in the prevention of thromboembolic events in medical patients with cardiopulmonary diseases. *Ann Hematol*, 1998, 76 (Suppl 1) A93 (abstract).

Harenberg J, Schomaker U, Flosbach CW, et al. Enoxaparin is superior to unfractionated heparin in the prevention of thromboembolic events in medical patients at increased thromboembolic risk. *Blood*. 1999 (Suppl 1):399a.