



Thrombosis Management: Long-Term Care Perspective

Laurie G. Jacobs, MD, Edith Nutescu, PharmD, and David A. Smith, MD, FAAFP, CMD

The Annual Meeting of the American Medical Directors Association was held March 6-9, 2003, in Orlando, Florida. At a symposium entitled, "Thrombosis Management: Long-Term Care Perspective," three speakers described the risk factors for development of thrombosis, the use and dosing of low-molecular-weight heparin, and the need for antithrombotic therapy protocols in the long-term care setting.

Deep Venous Thrombosis in Medical Patients: Prevention and Treatment

Laurie G. Jacobs, MD, is Associate Professor of Clinical Medicine and Head of the Unified Division of Geriatrics at New York's Albert Einstein College of Medicine and Montefiore Medical Center. Dr. Jacobs spoke about the pathophysiology of venous thromboembolism (VTE), risk factors, and the appropriate duration of antithrombotic therapy.

The most serious forms of VTE are deep venous thrombosis (DVT) and pulmonary embolism (PE). A less serious form, *superficial thrombosis*, usually requires only symptomatic treatment. In contrast, DVT can cause significant morbidity by leading to recurrent DVT, chronic venous insufficiency, postphlebotic syndrome, and venous stasis ulcers. Distal vein thrombosis can propagate proximally, and proximal DVT can embolize. Pulmonary embolism is often fatal.

The annual incidence of DVT in community-dwelling people is 48 per 100,000, and PE occurs in 23 per 100,000.¹ Although the risk of VTE is highest in hospitalized patients, the risk for nursing home residents is also substantial—10 times that of elderly people living outside nursing homes. Simply growing older increases the risk of VTE. In both men and women, the incidence of DVT and/or PE increases approximately 200-fold between the ages of 20 and 80 years.²

Because DVT is often asymptomatic or causes only subtle symptoms, it may not be easily recognized in all cases. However, Dr. Jacobs explained, "Understanding the pathophysiology of DVT will lead you to think about which patients are at risk." Three components contribute to the development of DVT: venous stasis, intimal injury, and hypercoagulability.

Venous stasis can be caused by venous obstruction, increased central venous pressure, venous dilatation, or immobility. Hospitalized patients and those admitted to nursing homes are often immobile due to disease or to the restrictions imposed by intravenous catheters

or monitoring devices. Intimal injury can be caused by surgery, venous catheter insertion, or trauma. Causes of hypercoagulability include acute infection, transfusion, nephrotic syndrome, and genetic conditions such as deficiency of a coagulation inhibitor (ie, antithrombin, protein C, or protein S). In patients with Factor V Leiden, another genetic cause of hypercoagulability, the initial thrombotic event may occur during older adulthood.

Malignancies can cause intimal injury, venous stasis, and hypercoagulability. The risk of DVT is higher in patients with gastric, lung, or pancreatic cancer, and lower in those with breast or prostate cancer. Chemotherapy further increases the risk of developing DVT. Patients with ischemic stroke and lower extremity hemiparesis are at high risk; the incidence of DVT in this population is 55%. Other risk factors include recent myocardial infarction, congestive heart failure (CHF), chronic obstructive pulmonary disease, obesity, and previous DVT. The risk of recurrent DVT is especially high in the first year after the initial event.

Surgery and trauma carry the highest risk of DVT, but immobilization and other risk factors are usually more common in the long-term care setting. Many patients—especially nursing home residents—have multiple conditions and circumstances that can lead to DVT.

Dr. Jacobs indicated that each institution should have guidelines for identifying patients at risk, as well as a policy for providing prophylactic therapy. Nonpharmacologic prophylactic measures include intermittent pneumatic compression devices, compression stockings, leg elevation, and early mobilization. Aspirin may be appropriate for prophylaxis of arterial thrombosis, but is not adequate for prevention of venous thrombosis because venous clot formation involves fewer platelets than does arterial clot formation. Bleeding can be especially problematic in patients who have an epidural catheter, and the use of anticoagulants in these patients requires careful consideration.

"For medical patients," said Dr. Jacobs, "low-dose unfractionated heparin and low-molecular-weight heparin are the

Supplement to

standard of care.” Unfractionated heparin (UH) and low-molecular-weight heparin (LMWH) are glycosaminoglycans, and both contain a pentasaccharide segment that allows them to interact with factor Xa. However, UH and LMWH differ in their ability to interact with thrombin. UH interacts with factor Xa and thrombin in a 1:1 ratio, while LMWH interacts with factor Xa and thrombin in a 4:1 ratio to 2:1 ratio.

LMWH and UH are effective agents for DVT prophylaxis in patients with ischemic stroke. The reduction in relative risk is 58% in patients treated with LMWH and 56% in those treated with low-dose UH.³ Similar reductions in relative risk are seen in medical patients who are given prophylactic LMWH or low-dose UH. This population includes patients with conditions such as CHF, chronic obstructive pulmonary disease, malignancy, or infection.

The thromboprophylactic efficacy of the LMWH enoxaparin was evaluated in a large trial of hospitalized patients who had class III or IV CHF or respiratory failure that did not require mechanical ventilation.⁴ The study also included patients who had an acute rheumatic disorder or an episode of inflammatory bowel disease, and had at least one other risk factor for VTE. Each patient was randomly assigned to receive 20 mg or 40 mg of enoxaparin or placebo once daily for 6-14 days. DVT was confirmed by venography or venous ultrasound. While the incidence of DVT was similar in the placebo and 20-mg enoxaparin groups, the 40-mg enoxaparin group had a 63% reduction in relative risk. In addition, the 40-mg enoxaparin group had a lower mortality rate during the 3-month follow-up period, indicating that early and effective prophylaxis is important in preventing death.

Turning to the topic of therapy for DVT, Dr. Jacobs explained that treatment patterns are changing. Instead of being admitted to the hospital for treatment with intravenous heparin, patients with DVT are now being treated with LMWH in the community or in the long-term care setting. Loading doses of warfarin are no longer used. Instead, estimated maintenance doses of warfarin are begun when LMWH therapy is initiated. Warfarin and LMWH are given concurrently until the international normalized ratio (INR) is sustained at a therapeutic level for 2 consecutive days. LMWH can then be discontinued.

According to the American College of Chest Physicians guidelines for therapy following a thrombotic event, warfarin should be continued for 3-6 months in patients with reversible or time-limited risk factors, for at least 6 months in patients with a first event of idiopathic VTE, and indefinitely in patients with recurrent DVT or irreversible risk factors such as cancer or congenital deficiency of a coagulation inhibitor.⁵

In summary, effective management of VTE in the long-term care setting hinges on an understanding of the pathophysiology of the disease and its risk factors. Identifying patients at risk is the first step in preventing and managing VTE.

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Special Populations: Debunking the Myth

Edith Nutescu, PharmD, is Clinical Assistant Professor of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy. She is also Director of the Antithrombosis Clinic, and Assistant Director of the Ambulatory Care and Wellness Center at the University of Illinois at Chicago Medical Center. Dr. Nutescu described laboratory monitoring for LMWH and discussed LMWH dosing in patients who are obese or have renal impairment.

“One of the major advantages of LMWH over traditional heparin is that LMWH does not require monitoring of its anti-coagulant effect,” Dr. Nutescu said. Laboratory monitoring is unnecessary because in general populations, the dose-response relationship of LMWH is predictable. However, the speaker explained, the pharmacokinetics of LMWH may be altered in certain populations including children, pregnant women, obese patients, and patients with renal impairment. Because these patients may require dose adjustment, laboratory monitoring may be helpful.¹

Laboratory monitoring of LMWH is accomplished by measuring the level of anti-Xa activity in plasma. The assay is product-specific, which means that it must be calibrated using the same type of LMWH that the patient is receiving. Testing is done after the drug has reached steady state—usually after the second or third dose. The blood specimen for anti-Xa testing should be collected when the peak plasma concentration is reached, 4 hours after a dose is given. Results are reported in units per milliliter of plasma (U/mL).

For prophylaxis, LMWH is given in lower doses—40 mg enoxaparin once daily or 30 mg twice daily—and the target range for anti-Xa activity is 0.2-0.6 U/mL. A more conservative range of 0.2-0.4 U/mL is sometimes used. In contrast, treatment doses of enoxaparin are higher and are based on the patient’s body weight in kilograms. The standard therapeutic regimen for enoxaparin is 1.5 mg/kg once daily or 1 mg/kg twice daily. The corresponding target ranges for anti-Xa activity are 1.0-2.0 U/mL for once-daily dosing and 0.5-1.2 U/mL for twice-daily dosing.

For long-term care patients who have DVT and are obese or have renal impairment, the key question is whether standard, weight-based doses of LMWH provide adequate levels of efficacy and safety. To examine the issue of standard versus adjusted dosing, Dr. Nutescu reviewed both pharmacokinetic and clinical outcomes data.

In a study comparing the pharmacokinetic characteristics of enoxaparin in obese and nonobese volunteers, each subject received a standard dose—1.5 mg/kg once daily—for 4 days.² There were no clinically significant differences between the groups in peak anti-Xa levels or in time to elimination of the drug, indicating that dose adjustment is not needed for individuals weighing up to 144 kg (body mass index, 48 kg/m²).

Clinical data also support the use of standard rather than adjusted doses of enoxaparin in obese patients with DVT. Data derived from clinical studies in which subjects received enoxaparin in a standard dose—1 mg/kg twice daily—revealed no difference between obese (up to 159 kg) and nonobese patients in efficacy (incidence of death, myocardial infarction, or need for urgent revascularization) or safety outcomes (major bleeding complications).³ However, for obese patients with DVT, the twice-daily dosing regimen is more effective than the once-daily regimen, as shown by the results of a study in which the incidence of DVT recurrence was about 50% lower in the group that received enoxaparin twice daily.⁴

Dr. Nutescu discussed the use of enoxaparin in patients with renal impairment. Because LMWH is cleared renally, it can accumulate in patients with renal dysfunction. Renal impairment is common in the long-term care setting, in part because the creatinine clearance rate decreases as age increases.

In a pharmacokinetic study of 40 mg enoxaparin given once daily to patients with varying degrees of renal impairment, drug accumulation increased as the level of renal function decreased.⁵ Patients with severe renal impairment (creatinine clearance rate less than 30 mL/min) had drug accumulation that was about 40% higher than the level seen in patients with mild renal impairment. The increased accumulation was also reflected in higher anti-Xa levels in plasma.

Clinical studies indicate the significance of drug accumulation. In studies comparing enoxaparin with UH, patients in the enoxaparin group received standard doses, while patients in the UH group received doses adjusted according to the results of activated partial thromboplastin times (APTTs).⁶ Despite dose adjustment in the UH group, renally impaired patients in both the UH and enoxaparin groups had significantly higher rates of bleeding and mortality than patients who did not have renal impairment.

Summarizing these findings, Dr. Nutescu said that enoxaparin dose adjustment is not required for obese patients weighing up to 160 kg. However, dose adjustment is required to reduce the risk of bleeding in patients with renal impairment.⁷ For patients with creatinine clearance rates below 30 mL/min,

the enoxaparin dose should be reduced by 40% to 0.6 mg/kg twice daily. For patients with creatinine clearance rates in the range of 30–60 mL/min, the dose should be reduced by 20% to 0.8 mg/kg twice daily. Both of these dosing regimens provide therapeutic levels of anti-Xa activity.

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Coagulating the Efforts of Consultant Pharmacists and Medical Directors in Long-Term Care

David A. Smith, MD, FAAFP, CMD, is Professor of Family Medicine at the Texas A&M University College of Medicine in College Station. Dr. Smith focused on collaboration and preparedness as fundamental components of quality in the long-term care setting.

Dr. Smith began by describing the responsibilities of consultant pharmacists and medical directors in long-term care facilities. The consultant pharmacist consults on all aspects of pharmacy services, establishes a system of record keeping for controlled drugs, validates controlled-drug records, reviews the records of each nursing home resident monthly, and reports irregularities that must be acted upon to the attending physician and director of nursing. The medical director is responsible for implementation of resident care policies and coordination of medical care in the facility.

Clinical conditions that may warrant anticoagulant prophylaxis or treatment are common in the long-term care setting. These conditions include orthopedic procedures, valvular heart disease or prosthetic heart valves, atrial fibrillation, DVT, and PE. A number of factors should be considered when assessing

whether a long-term care resident is a candidate for antithrombotic therapy, such as:

- Risk of thrombotic event
- Risk of bleeding event
- Risk of falling or other trauma
- Mental status and safety awareness
- Expected compliance with medication regimen and laboratory monitoring
- Life expectancy and quality of life
- Cost-benefit ratio

Dr. Smith discussed the area of anticoagulant therapy as an example of how consultant pharmacists and medical directors can collaborate to improve the quality of medical care. The first step is to be ready to evaluate and act when a thrombotic event occurs. "You need to be pre-

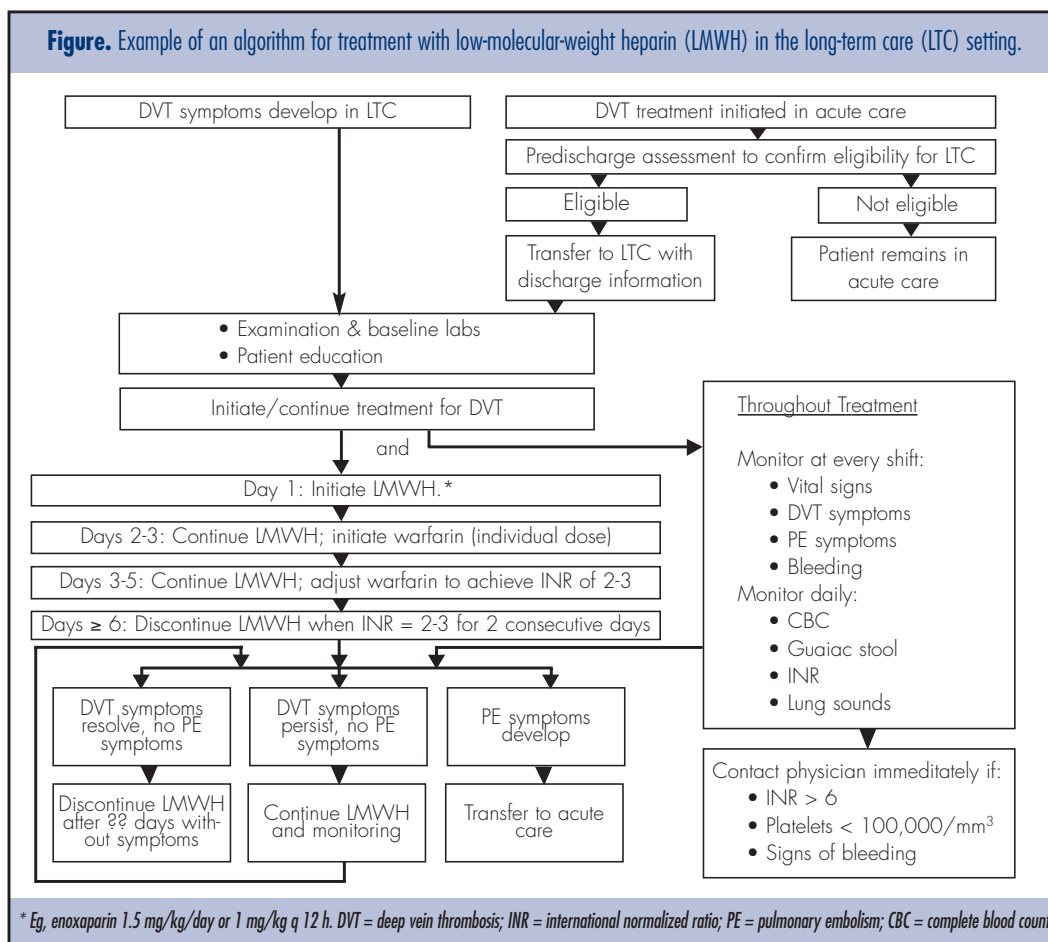
pared; you need to have your policies, procedures, and algorithms in place," Dr. Smith said. The facility should have a protocol that defines candidates for therapy, drugs to be used, when therapy should be given, and the route, monitoring, and duration of therapy. The protocol can be designed as an algorithm that encompasses all phases of therapy (Figure).

Consultant pharmacists and medical directors can also collaborate to provide education for the facility's nursing staff. Nurses and certified nursing assistants are front-line personnel in patient care. Educating nurses about the clinical indications for antithrombotic therapy enables them to help clinicians identify patients who may benefit from therapy. Nurses should also be educated about drug interactions and adverse drug reactions (ADRs), and should be familiar with the facility's protocols for anticoagulation therapy. Certified nursing assistants should be educated to recognize changes in condition that may signal a thrombotic event or anticoagulant mishap. Education and systematic drug review are the keys to anticipating drug interactions and ADRs.

What do attending physicians want from the consultant pharmacist regarding drug selection? Dr. Smith stated that physicians want scientific facts and reference-based advice, statements about clinical relevance and the likelihood of adverse effects, honest representations of economic factors, and management options.

Attending physicians should be able to interact directly with the consultant pharmacist, and both parties should bring any problems to the medical director. In the long-term care setting, collaboration and the use of science-based protocols enhance the quality of health care.

Figure. Example of an algorithm for treatment with low-molecular-weight heparin (LMWH) in the long-term care (LTC) setting.



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