

Low-Molecular-Weight Heparin in Outpatient Treatment of DVT

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Patients with a diagnosis of acute deep venous thrombosis have traditionally been hospitalized and treated with unfractionated heparin followed by oral anticoagulation therapy. Several clinical trials have shown that low-molecular-weight heparin is at least as safe and effective as unfractionated heparin in the treatment of uncomplicated deep venous thrombosis. The use of low-molecular-weight heparin in an outpatient program for the management of deep venous thrombosis provides a treatment alternative to hospitalization in selected patients. Use of low-molecular-weight heparin on an outpatient basis requires coordination of care, laboratory monitoring, and patient education and participation in treatment. Overlapping the initiation of warfarin permits long-term anticoagulation. Advantages include a decreased incidence of heparin-induced thrombocytopenia and fewer episodes of bleeding complications. Future clinical trials evaluating the safety and efficacy of low-molecular-weight heparin in the treatment of complicated deep venous thrombosis will further define appropriate indications for use and strategies for outpatient management.

Each year, members of two different medical faculties develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family Practice at the University of Kentucky College of Medicine, Lexington. Guest editors of the series are Bryan F. Yeager, Pharm.D., Thomas Armsey, M.D., and Samuel C. Matheny, M.D., M.P.H.

Deep venous thrombosis (DVT) is associated with more than 600,000 hospitalizations annually in the United States and results in more than 200,000 deaths caused by pulmonary embolism.¹ Patients with a diagnosis of acute DVT have traditionally been hospitalized and treated with a continuous infusion of unfractionated heparin for five to 10 days, followed by oral anticoagulation therapy for at least three months. Hospitalization has traditionally been considered necessary because of concerns about fatal pulmonary embolism (and the need for careful laboratory monitoring), but this risk is now known to be low during the initial treatment of DVT.² Because of the wide variability in anticoagulant response among patients treated with unfractionated heparin, frequent monitoring of the activated partial thromboplastin time (aPTT) and dosage adjustments are required to keep anticoagulation in the therapeutic range. In most

patients who have no major risk factors for bleeding or subsequent pulmonary embolism, such as protein C or S deficiency, history of previous pulmonary embolism or more proximal DVT, hospitalization is necessary only for monitoring aPTT and adjusting unfractionated heparin therapy.

Several clinical trials have shown that low-molecular-weight heparins are at least as safe and effective as unfractionated heparin in the treatment of DVT.³⁻⁶ These agents have a longer half-life and a more predictable anticoagulant response than unfractionated heparin, which allows for subcutaneous administration without laboratory monitoring.⁷ The use of low-molecular-weight heparins in the treatment of DVT provides an opportunity to realize significant cost savings by preventing or shortening hospitalization and by increasing patient comfort and satisfaction with health care.⁸ Shifting the management of DVT to the ambulatory setting presents several clinical and logistical challenges for clinicians, administrators and patients. The success of an outpatient program for the management of DVT depends on familiarity with currently available low-molecular-weight heparins, patient selection, protocol development and outcome evaluation.

The risk of fatal pulmonary embolism during the initial treatment of DVT is lower than was previously believed.

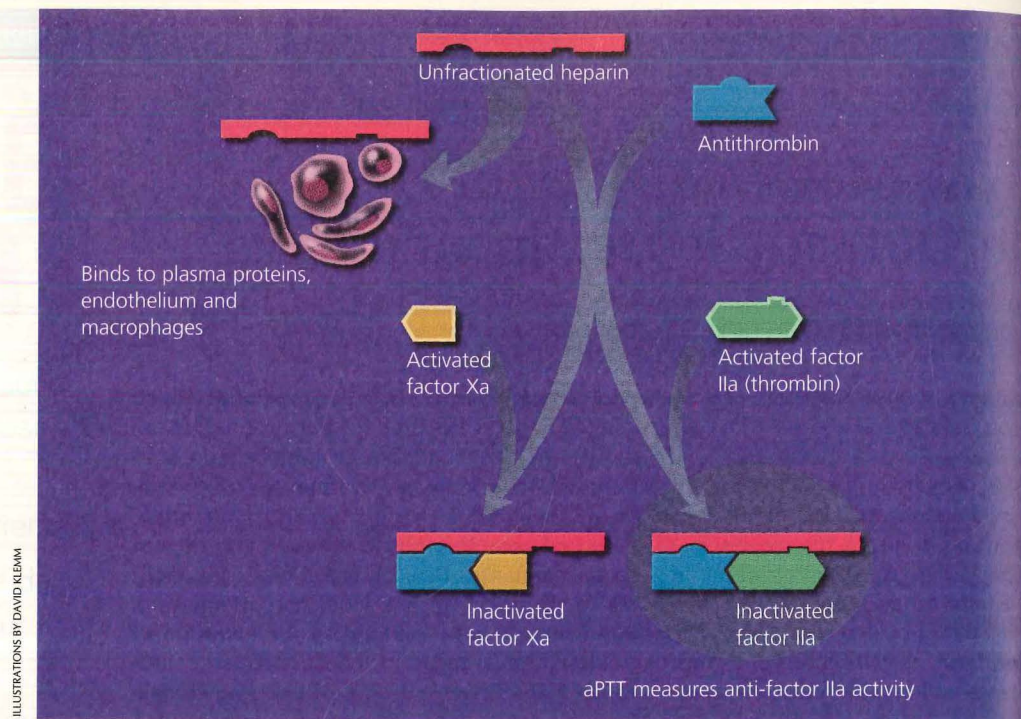


FIGURE 1A. Effect of low-molecular-weight heparin (LMWH) and unfractionated heparin on factor IIa and factor Xa. Both types of heparin inactivate factor Xa by interacting with antithrombin. Longer chain, unfractionated heparin (UFH) is able to inactivate factor IIa through formation of a tertiary complex, unlike LMWH. Compared with LMWH, UFH binds more to plasma proteins, endothelium and macrophages, resulting in reduced bioavailability and greater patient variability to a given dose. UFH inactivates factors IIa and Xa and affects the aPTT, a measure of anti-factor IIa activity. (aPTT = activated partial thromboplastin time)

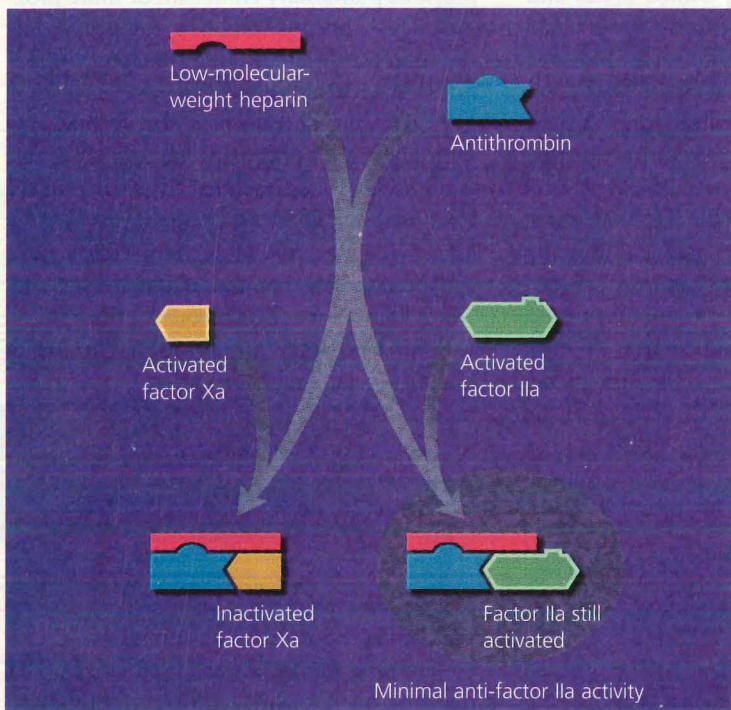


FIGURE 1B. Low-molecular-weight heparin inhibits factor Xa and minimally affects factor IIa; thus activated partial thromboplastin time is not used to measure its anticoagulant activity.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins are derived from depolymerization of standard heparin, which yields fragments approximately one third the size of the parent compound. These lower-molecular-weight fractions have several properties that differentiate them from unfractionated heparin. Low-molecular-weight heparins exert their anticoagulant effect by inhibiting factor Xa and augmenting tissue-factor-pathway inhibitor but minimally affect thrombin, or factor IIa (*Figure 1a and 1b*). Thus, the aPTT, a measure of antithrombin (anti-factor IIa) activity, is not used to measure the activity of low-molecular-weight heparins, which requires instead a specific anti-Xa assay.

In addition to having lower antithrombin activity than unfractionated heparin, low-molecular-weight heparins bind less to plasma proteins, endothelium and macrophages, permitting greater bioavailability and little inter-patient and intra-patient variability in response to a given dosage.⁹ Clinical trials have confirmed that effective antithrombotic

activity can be consistently achieved by calculating dosages based on body weight without the need for laboratory monitoring.¹⁰

Since these agents are eliminated primarily through the kidneys, accumulation of anti-factor Xa activity may occur in patients with chronic renal insufficiency. Plasma anti-factor Xa concentrations should be monitored in patients with renal dysfunction and possibly in those weighing less than 50 kg (110 lb) or more than 80 kg (176 lb).¹⁰ Low-molecular-weight heparins also appear to be associated with less bleeding and a decreased frequency of heparin-induced thrombocytopenia, as a result of their lower affinity for platelets and von Willebrand factor.¹⁰ Danaparoid (Orgaran) and lepirudin (Refludan) are indicated in the treatment of heparin-induced thrombocytopenia type II. Lepirudin is a recombinant form of hirudin, an anticoagulant derived from the saliva of leeches. Danaparoid is a low-molecular-weight heparin composed of a mixture of heparan, dermatan and chondroitin sulfates.

Low-molecular-weight heparins currently available in the United States include enoxaparin (Lovenox), dalteparin (Fragmin) and ardeparin (Normiflo), while nadroparin (Fraxiparine), tinzaparin (Logiparin, Innohep) and reviparin (Clivarine) are marketed elsewhere (Table 1). Enoxaparin was recently labeled by the U.S. Food and Drug Administration for outpatient treatment of DVT and may also be used in the inpatient setting to manage DVT with or without pulmonary embolism. Each of these agents is prepared with a different method of depolymerization, resulting in distinct molecular weights (4,000 to 5,500 Da) and relative effects on factor Xa and thrombin. For this reason, low-molecular-weight heparins are unique and not necessarily therapeutically interchangeable, although their pharmacologic and clinical characteristics are similar.¹⁰

Several meta-analyses have indicated that low-molecular-weight heparins are superior to unfractionated heparin in the treatment of

Low-molecular-weight heparin is associated with less bleeding and fewer episodes of heparin-induced thrombocytopenia than unfractionated heparin.

patients with established DVT. One analysis did not indicate a significant difference in symptomatic recurrence rates or adverse events but did note trends favoring low-molecular-weight heparins.¹¹ The safety and effec-

TABLE 1
Comparison of Low-Molecular-Weight Heparins

Agent	Clinical trial treatment doses (anti-Xa units)	Average molecular weight (Da)	Intravenous half-life (minutes)	Cost*
Ardeparin (Normiflo)†	Not evaluated	6,000	200	\$154.50‡
Dalteparin (Fragmin)†	100 U per kg twice daily	5,000	119 to 139	63.00§
Enoxaparin (Lovenox)†	100 U per kg twice daily	4,500	129 to 180	78.50
Nadroparin (Fraxiparine)	225 U per kg twice daily	4,500	132 to 162	NA
Reviparin (Clivarine)	100 U per kg twice daily	4,300	NA	NA
Tinzaparin (Logiparin, Innohep)	175 U per kg once daily	4,900	111	NA
Danaparoid II (Orgaran)	750 U twice daily	5,500	24 hours	237.00§

Anti-Xa = plasma anti-factor Xa; Da = dalton (atomic mass unit); NA = not available.

*—Unless otherwise noted, estimated cost to the pharmacist for one day's therapy, rounded to the nearest half dollar, based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 1998. Cost to the patient will be higher, depending on prescription filling fee.

†—Available in the United States.

‡—Price given is for 10 vials of medication (5,000 units per 0.5 mL). No dosing recommendation is given.

§—Price given is for treatment of a 70-kg (154-lb) adult.

||—Indicated for heparin-induced thrombocytopenia only.

Information from references 9 and 10.

tiveness of these agents were significantly better than that of unfractionated heparin in two other analyses.^{12,13} Collectively, the results reveal a statistically significant reduction in thrombus size, recurrent venous thromboembolism, major bleeding events and pooled long-term mortality rate. Although the lower mortality rates observed in these trials were mostly attributable to a subgroup of patients with cancer, the data may indicate greater efficacy of low-molecular-weight heparins in this high-risk population.¹⁴

Two recent studies of patients with DVT have also been conducted to compare the effect of low-molecular-weight heparins given on an outpatient basis subcutaneously twice daily with that of unfractionated heparin given by continuous intravenous infusion in the hospital.^{15,16} No significant difference was found in rates of recurrent venous thromboembolism, hemorrhagic complications, development of thrombocytopenia or mortality. Low-molecular-weight heparins were as safe and effective as unfractionated heparin, and most patients were managed at home immediately after diagnosis or a brief hospitalization.

In addition to comparable efficacy in the treatment of DVT, patients receiving low-molecular-weight heparin reported a higher quality of life in terms of physical and social function and sense of well-being. Treatment of DVT with low-molecular-weight heparin

TABLE 2
Exclusion Criteria for Outpatient Therapy with Low-Molecular-Weight Heparin

Clinical evidence of pulmonary embolism or suspected embolism
Conditions that increase the risk of bleeding: <ul style="list-style-type: none">Recent surgeryPeptic ulcer diseaseMalignant hypertensionIncreased risk of falling
High risk of recurrent thrombosis: <ul style="list-style-type: none">Extensive proximal deep venous thrombosisRecurrent deep venous thrombosisPregnancyProtein C or S deficiency
Likelihood of noncompliance
Unavailable for follow-up
Inadequate home support system

Information from references 14 and 15.

was more cost-effective than therapy with unfractionated heparin because the length of the hospital stay was reduced by 60 to 70 percent without an increase in the cost of home health care.

Patient Selection

Criteria are needed for the selection of patients who may be candidates for low-molecular-weight heparin therapy on an ambulatory basis. The studies^{15,16} evaluating the effectiveness of low-molecular-weight heparins in the treatment of DVT excluded certain patient populations (*Table 2*). Based on selection criteria from these clinical trials, approximately 40 percent of all patients diagnosed with DVT would be eligible for home-based treatment with low-molecular-weight heparin.^{15,16}

While the safety and efficacy of low-molecular-weight heparin in the treatment of patients with DVT alone is clear, controversy surrounds its use in the hospital and at home in patients with documented or suspected pul-

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monary embolism. A recent study¹⁷ evaluating once-daily administration of tinzaparin compared with unfractionated heparin in the treatment of acute pulmonary embolism found no difference in rates of combined recurrent thromboembolism, major bleeding or death. However, low-molecular-weight heparin was not given on an outpatient basis in that study, and the results cannot be extrapolated to patients who take these agents at home.

The Columbus study¹⁸ compared low-molecular-weight heparin, given twice daily, with unfractionated heparin in patients with DVT, with or without pulmonary embolism or history of venous thromboembolism. Twenty-seven percent of the patients who were randomized to the low-molecular-weight heparin arm of this trial were managed outside the hospital. Both treatment groups were similar in the incidence of recurrent thromboembolic events, episodes of major bleeding and mortality. While further study is warranted to determine if patients with DVT and suspected pulmonary embolism may be safely and effectively treated with low-molecular-weight heparin in the ambulatory setting, the evidence in favor of this therapy is mounting rapidly.¹⁹ At present, outpatient low-molecular-weight therapy is best reserved for use in patients with uncomplicated DVT, a competent caregiver at home or the ability for self-care, and an appropriate mechanism for follow-up with their family physician (Figure 2).

Development of Protocol

A multidisciplinary approach is necessary to develop the specific details of an outpatient management protocol for DVT. Physicians, nurses, pharmacists and other health care professionals each contribute a unique perspective in planning and implementing a program protocol for managing patients with low-molecular-weight heparin therapy on an outpatient basis.

In addition to cost, drug selection and other pharmaceutical factors should be discussed before protocol implementation.²⁰ No

evidence indicates that any one low-molecular-weight heparin is more effective or safer than another in the treatment of DVT on an outpatient basis. Drug selection is often dictated by ease and frequency of administration, cost and evaluation of the safety and efficacy of each agent based on the results of clinical trials.

All low-molecular-weight heparins are packaged in syringes containing smaller, prophylactic doses, so repackaging is necessary to provide the appropriate treatment dosage as a single injection. New unit-dose syringes for several agents used for the treatment of DVT have just been approved or are awaiting FDA approval. Information about the stability and compatibility of low-molecular-weight heparins should be obtained from the manufacturer or other sources to ensure proper preparation and storage of these agents. These agents may be dispensed by outpatient pharmacies to patients for self-administration at home or prepared by home health care professionals delivering care directly to the patient.

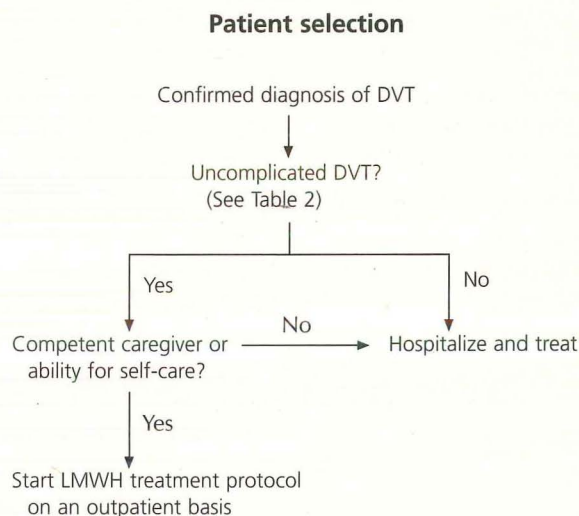


FIGURE 2. Algorithm for the selection of patients for low-molecular-weight heparin therapy of deep venous thrombosis. (DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin)

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