

# ASHP Therapeutic Position Statement on the Use of Low-Molecular-Weight Heparins for Adult Outpatient Treatment of Acute Deep-Vein Thrombosis

## Statement of Position

The American Society of Health-System Pharmacists believes that the use of low-molecular-weight-heparin (LMWH) therapy for the treatment of acute deep-vein thrombosis (DVT) in appropriate adult outpatients is as safe and effective as traditional inpatient therapy with unfractionated heparin (UFH). Outpatient treatment of acute DVT with LMWHs is often more cost-effective than traditional inpatient therapy and is associated with greater patient satisfaction. When opportunities exist, health care professionals are encouraged to actively participate in developing, implementing, and monitoring outpatient DVT treatment programs.

## Background

Traditionally, patients who are diagnosed with acute DVT are hospitalized for administration and monitoring of intravenous UFH therapy. Warfarin sodium is overlapped with UFH for a minimum of five days until the patient's International Normalized Ratio (INR) is therapeutic for two consecutive days, at which time UFH can be discontinued.<sup>1</sup> LMWHs have several unique properties that may offer advantages over UFH in the initial treatment of DVT, including a more predictable anticoagulant response, a longer plasma half-life, and reduced frequencies of thrombocytopenia and osteopenia.<sup>1</sup> Three LMWHs are currently available in the United States (Table 1).<sup>2-5</sup> Pharmacokinetic and pharmacodynamic properties vary among LMWHs, and data are insufficient to determine whether these agents are clinically interchangeable.<sup>6,7</sup>

The goals of outpatient treatment of DVT are the same as those of traditional inpatient treatment: arrest thrombus growth, prevent recurrence, limit limb swelling, and prevent embolization and the postphlebotic syndrome. Outpatient therapy has the added benefits of decreasing overall DVT treatment costs and improving quality of life.<sup>8</sup>

## Evidence of Efficacy and Safety

Randomized controlled clinical trials comparing LMWHs with UFH for the treatment of acute DVT in hospitalized patients suggest that LMWH therapy is at least as safe and effective as conventional UFH therapy (Table 2).<sup>9-17</sup> LMWHs are administered in weight-based, individualized doses and do not require routine frequent monitoring of activated partial thromboplastin time (aPPT). Although thrombocytopenia occurs infrequently with LMWHs, a platelet count measured between days 5 and 7 of therapy is helpful in monitoring for the occurrence of heparin-induced thrombocytopenia in heparin-naïve patients.<sup>1</sup>

Clinical trials comparing LMWHs administered in the outpatient setting with conventional inpatient UFH therapy have demonstrated that both were equally safe and effective for acute DVT in appropriately selected patients.<sup>9,11,18,19</sup> Levine et al.<sup>9</sup> reported that patients with proximal DVT randomized to treatment with traditional UFH in the hospital and

those randomized to outpatient treatment with enoxaparin 1 mg/kg subcutaneously every 12 hours did not have significant differences in rates of recurrent thromboembolism or major bleeding. The rate of recurrent thromboembolism was 6.7% in the UFH group and 5.3% in the enoxaparin group.

Evidence that outpatient LMWH therapy is as safe and effective as inpatient UFH therapy was also provided by an international, multicenter, randomized, controlled trial involving nadroparin.<sup>18</sup> The LMWH was as effective as UFH therapy, cost less, and had few or no measurable adverse effects on physical or mental well-being. A systematic review also suggested that outpatient treatment of DVT with LMWHs is efficacious and safe.<sup>20</sup>

The success of outpatient DVT treatment programs in many health care systems demonstrates that acute DVT may be safely and effectively managed in everyday clinical practice outside the hospital setting.<sup>12,13,19</sup> In fact, the strength of available literature supporting the use of LMWHs in the treatment of acute DVT has led to a reevaluation of the use of UFH for this indication. Guidelines from the American College of Chest Physicians (ACCP) state that "LMWH offers the major benefits of convenience of dosing and facilitation of outpatient treatment."<sup>11</sup> ACCP recommends that LMWHs be preferred over UFH for the treatment of acute DVT or pulmonary embolism (PE). Evidence supporting outpatient treatment of PE with LMWHs exists but is less robust than that for outpatient treatment of DVT.<sup>12,21,22</sup>

## Cost-Effectiveness

Hospitalization adds appreciably to the cost of treating acute DVT. Even though LMWH drug costs are much higher than those of UFH, avoiding hospitalization or decreasing its length substantially lowers the overall cost of DVT treatment.

An economic evaluation of an existing outpatient DVT treatment program in a large group-model health maintenance organization (HMO) revealed an average cost saving of \$2828 (in 1998 dollars) for each patient treated at home with LMWHs.<sup>13</sup> Another retrospective pharmacoeconomic evaluation of outpatient DVT treatment with LMWHs in a large HMO documented a mean cost difference of \$2583 per patient in favor of the LMWH group.<sup>23</sup> These savings are consistent with previously published data from a non-managed care environment that estimated the saving associated with outpatient treatment of DVT at \$2750 per patient (in 1998 dollars).<sup>8</sup> A trial of the inpatient administration of LMWHs versus UFH for DVT found that the average cost saving per patient treated with LMWHs was \$509 (in 1998 dollars).<sup>24</sup> The authors estimated that if 37% of the patients receiving LMWHs had been treated as outpatients, the average cost saving per patient would have increased to \$1159. By a similar analysis, if 92% of the LMWH-treated patients had received the therapy as outpatients, the cost saving would have been \$2165 per patient.

During a two-year evaluation period, the previously mentioned group-model HMO realized a total cost saving of

Table 1.  
Heparin Profiles<sup>a</sup>

Variable	Unfractionated Heparin <sup>2</sup>	Dalteparin <sup>3,b</sup>	Enoxaparin <sup>4,c</sup>	Tinzaparin <sup>5,d</sup>
Mean molecular weight	15,000	5,000	4,500	5,500–7,500
Bioavailability	30–60	81–93	92	86.7
Plasma half-life (min) <sup>e</sup>	45–60	119–139	129–180	204–210
Dosage recommendations for DVT <sup>f</sup>	Various	200 international units/kg subcutaneous once daily or 100 international units/kg subcutaneous q 12 hr for 5–7 days in conjunction with warfarin	1 mg/kg subcutaneous q 12 hr or 1.5 mg/kg once daily <sup>g</sup> for 5–7 days in conjunction with warfarin	175 international units/kg subcutaneous once daily for 5–7 days in conjunction with warfarin

<sup>a</sup>DVT = deep-vein thrombosis.<sup>b</sup>Lacks FDA-approved labeling for use in the treatment of DVT or pulmonary embolism (PE).<sup>c</sup>FDA has approved labeling for use in inpatient treatment of acute DVT with or without PE or for outpatient treatment of acute DVT without PE.<sup>d</sup>FDA has approved labeling for use in the inpatient treatment of acute DVT with or without PE.<sup>e</sup>Inpatients with normal renal function.<sup>f</sup>Based on actual body weight; dosing for patients weighing >120 or <40 kg is controversial (anti-Xa activity monitoring has been suggested for these patients).<sup>g</sup>Once-daily administration may be less effective in very obese patients and patients with cancer.Table 2.  
Adverse Outcomes of Treatment of Deep-Vein Thrombosis with Low-Molecular-Weight Heparins and Unfractionated Heparin (UFH)

Outcome	Frequency (%)			
	UFH <sup>9,10</sup>	Dalteparin <sup>11,12</sup>	Enoxaparin <sup>9,13</sup>	Tinzaparin <sup>10</sup>
Death	6.7–9.6	1.2–7	4.3–4.6	4.7
Major bleeding	1.2–5	0.9–2	0.8–2.0	0.5
Pulmonary embolism	0.8–2.7	0.9	0.8–1.5	1.4
Recurrence of thrombus extension	4.1–5.9	1.6–3.6	2.6–4.5	1.4

over \$1 million (in 1998 dollars)—enough to offset the entire operating budget for a centralized clinical pharmacy anticoagulation service.<sup>13</sup> Sensitivity analysis demonstrated that the savings realized by this organization were robust. For example, tripling the acquisition cost of LMWHs would reduce the average cost saving to only \$1953 per DVT episode managed at home. Break-even analysis demonstrated that, for the cost of traditional inpatient treatment to equal outpatient treatment, either LMWH acquisition costs would have to increase by 750% or costs for inpatient therapy would have to decrease by 77%. Health systems should, therefore, explore outpatient treatment of DVT. The associated financial savings can offset the cost of developing, implementing, and maintaining the service.

Access to care, support by ancillary care providers, insurance coverage, patient satisfaction, and quality of life need to be considered to ensure that therapy can be obtained and be safe and effective. LMWH therapy can be a financial burden for patients who lack an outpatient prescription drug benefit; many insurance plans do not cover the cost of self-administered outpatient LMWH therapy. It is important to consider all aspects of care and to be aware that, in special situations, inpatient treatment of DVT may be preferable.

### Patient Satisfaction

Anecdotal experience and the results of formal evaluations indicate a high degree of patient satisfaction and comfort with outpatient DVT treatment. Using the Medical Outcomes Study Short-Form 36<sup>25</sup> to compare changes in health-related quality of life, O'Brien et al.<sup>8</sup> observed a greater improvement in social

functioning for patients treated with LMWHs as outpatients than for those treated with UFH as inpatients. These results are consistent with the findings of a separate study that used a 5-point Likert scale to determine that 91% of patients completing the survey were “very pleased” to have their DVT treated at home.<sup>19</sup>

### Successful Outpatient DVT Treatment Programs

The medical literature contains numerous reports of successful outpatient DVT treatment programs.<sup>12,13,19,23</sup> These programs have been implemented in a variety of health care systems and tailored to the needs and strengths of each system. Successful implementation of these programs relies on detailed care plans that begin at the point of entry into the system and on collaborative efforts by a variety of practitioners, departments, laboratory personnel, home care services, social workers, case managers, risk management personnel, and financial planners.

Before starting outpatient DVT therapy, practitioners should ensure that patients understand the implications of their disease and the rationale behind treatment. The correct use and potential adverse effects of LMWHs and warfarin should be thoroughly reviewed with patients. Patients should be taught to identify signs and symptoms of complications and to seek medical attention immediately should they occur. During initial therapy, frequent patient contact is essential for early detection of potential problems and to ensure that patients have their questions and concerns addressed promptly. Follow-up contact should be scheduled to ask patients about signs and symptoms that may suggest bleeding,

thrombus extension, and PE. Once LMWH therapy is completed (in approximately five to seven days), patient contact can be less frequent. Practitioners should document their patient care activities in the medical record. Occasionally, some patients are unwilling or unable to comply with the demands of outpatient DVT treatment. Outpatient treatment may still be accomplished by using home health nursing services, having patients come to the medical office for daily LMWH injections, or admitting patients to a skilled-nursing facility. The added costs incurred by these services still make outpatient treatment of DVT attractive compared with the cost of hospitalization.

### Special Patient Populations

Outpatient DVT treatment requires careful patient selection. There is no consensus yet about which patients are the best candidates for home therapy; a comparison of exclusion criteria used in outpatient DVT treatment programs is provided in Table 3.<sup>26</sup> In the opinion of the advocates of strict exclusion criteria, careful patient selection and risk stratification reduce the rate of thromboembolic complications.<sup>27</sup> Proponents of a less restrictive approach argue that strict exclusion criteria may unnecessarily withhold outpatient treatment with LMWHs from many patients. Further investigation is necessary to determine whether the lower rate of thromboembolic complications observed in programs with strict exclusion criteria represents a true reduction in the complication rate or a selection bias. For example, cancer patients with DVT are denied the option of outpatient therapy in some programs. However, preliminary Evidence suggests that the mortality rate among cancer patients treated with LMWHs is lower than

the rate among patients treated with UFH.<sup>28</sup> Recent evidence has also demonstrated that patients with cancer and DVT or PE had fewer recurrences of DVT when they were treated with an LMWH alone (dalteparin 200 International Units/kg subcutaneously once daily for one month, followed by 150 International Units/kg once daily for five months) than when they received usual therapy with an LMWH followed by oral anticoagulation therapy.<sup>29</sup> Outpatient DVT therapy with LMWHs also offers terminally ill cancer patients the opportunity to spend more time at home.

According to strict exclusion criteria, approximately 60% of patients with acute DVT are eligible for some form of outpatient LMWH therapy (Table 3). A less restrictive approach increases the fraction of eligible patients to 75–95% while maintaining the same efficacy and safety found in clinical trials.<sup>12,13,19</sup>

Patients with concomitant diseases that could affect LMWH pharmacokinetics may be less suitable candidates for outpatient DVT therapy. Altered pharmacokinetics (as in patients with renal dysfunction and pregnant patients) may result in insufficient or excessive anticoagulation, increasing the risk of therapeutic failure or bleeding. In these circumstances, outpatient therapy should be undertaken with caution, and vigilant monitoring for complications is indicated.

Plasma concentrations of LMWHs are not routinely monitored; however, anti-factor Xa activity can be measured and used to approximate the LMWH concentration in the blood. The College of American Pathologists reports that this assay is routinely performed in approximately 18% of all laboratories.<sup>30</sup> The minimal anti-Xa level needed for a therapeutic effect has not been established, but an inverse relationship between thrombus propagation and anti-Xa level

Table 3.

#### Outcomes of and Exclusion Criteria for Outpatient Deep-Vein Thrombosis (DVT) Treatment Programs

Variable	Ref. 26 ( <i>n</i> = 102)	Ref. 19 ( <i>n</i> = 89)	Ref. 12 ( <i>n</i> = 194)	Ref. 13 ( <i>n</i> = 391)
Exclusion criteria	Platelet count, <100 × 10 <sup>3</sup> /mm <sup>3</sup> Active bleeding History of gastrointestinal bleeding within 6 mo Underlying liver disorder History of familial bleeding disorder Hypertensive urgency or emergency Hypercoagulable state Catheter-associated DVT History of heparin sensitivity Pregnant or lactating Pulmonary embolism Iliofemoral thrombosis >30% of ideal body weight Renal insufficiency Recent surgery Other comorbid medical conditions Other factors increasing risk of home treatment	High risk of bleeding Additional medical condition requiring hospital admission Incapable of self-treatment at home	Concurrent illness requiring hospital admission for >48 hr Active bleeding Inpatient status without discharge in the next 48 hr Pulmonary embolism DVT with pain requiring i.v. narcotics Age, <18 yr Likelihood of poor compliance	Hospital admission required for concurrent symptomatic disease Pulmonary embolism Active bleeding Pregnant
Major bleeding complication rate (%)	0	1.1	2.1	0.8
Thromboembolic complication rate (%)	1.9	6.7	3.6	4.1
Outpatient treatment (%)	42 (61 with abbreviated hospital admission)	>75 (including <24-hr hospital admission)	95	78

has been observed.<sup>31,32</sup> Furthermore, high anti-Xa levels have been associated with bleeding.<sup>33</sup> The exact role of anti-Xa activity monitoring is currently not well defined. Monitoring anti-Xa activity has been suggested for patients who are small, obese, pregnant, or renally impaired, as well as for children.<sup>34</sup> Blood samples for measuring anti-Xa activity should be collected three to four hours after LMWH administration.<sup>30</sup> Therapeutic ranges of 0.6–1.0 and 1.0–2.0 International Units/mL have been suggested for twice-daily and once-daily LMWH therapy, respectively.<sup>34</sup> Inhibition of factor Xa is not the sole contributor to LMWH's anticoagulant effect. Adjusting LMWH dosages on the basis of anti-factor Xa activity is therefore difficult to justify.<sup>35</sup> In addition, dosage-adjustment algorithms similar to those used with UFH and aPTT measurements are not currently available for LMWH and anti-factor Xa measurements.

### Barriers to Outpatient Treatment with LMWHs

Some patients are unable or unwilling to self-inject LMWHs or cannot adhere to the rigorous schedule of blood drawings or finger sticks necessary for monitoring outpatient transition to oral warfarin therapy. Options for these patients include visiting-nurse services, admission to a skilled-nursing facility, and admission to the hospital. Point-of-care INR-monitoring devices for warfarin therapy may provide a means for patients who do not live close to a clinical laboratory or who have limited mobility.

LMWH therapy may be a financial burden for patients who do not have prescription drug insurance. As more successful programs are developed and the cost savings are appreciated, more broad-based coverage for outpatient DVT treatment may become available. Health care professionals should continue to document the clinical and financial outcomes associated with outpatient DVT treatment programs. Presenting favorable outcomes data to health plans may facilitate approval of coverage on a more widespread basis.

Commercially available doses do not always meet patient-specific needs, and some institutions have therefore elected to repackage weight-based LMWH doses. Repackaging LMWHs may be attractive from an economic perspective and for ease of administration; however, not all pharmacies are equipped with cleanrooms with laminar-airflow hoods or barrier isolators, which are necessary to ensure the sterility of repackaged LMWH syringes. Well-publicized reports of patients being harmed by compounded injectables substantiate that effective compounding practices must be followed to ensure the quality and safety of the product.<sup>36,37</sup> In addition, repackaged enoxaparin syringes must be refrigerated,<sup>38</sup> which may be problematic for patients who do not have ready access to a refrigerator. Repackaged dalteparin syringes have been shown to retain 90% of anti-Xa activity for 15 days at room temperature.<sup>39</sup>

Outpatient DVT therapy with LMWHs requires a well-coordinated system of communication and follow-up. Patients should have access to a provider 24 hours a day, seven days a week to address questions and concerns in a timely manner. This may present problems to health care systems that are inaccessible after hours or on weekends and holidays. The availability of an anticoagulation management service has been shown to be beneficial in the outpatient management of DVT.<sup>12,13,19</sup>

Elements of an outpatient LMWH therapy program can be considered without a dedicated anticoagulation management service providing 24-hour support. For example, a health system with limited resources can develop an outpatient LMWH treatment protocol through the combined efforts of primary care providers, affiliated urgent care centers, emergency department physicians, and health-system pharmacists and nurses. The protocol would clearly specify criteria for identifying appropriate candidates for the therapy and outline procedures for initial treatment and education, all of which could be the responsibility of the urgent care and emergency room physicians. Follow-up care during standard outpatient hours of operation can be provided by primary care providers or pharmacists and nurses trained and dedicated to monitoring outpatients who are receiving LMWHs for acute DVT. After-hours care can be managed by the provider's on-call service or emergency department. The overall coordination of care should be the responsibility of a designated health care professional, who should be notified as soon as possible following the decision to initiate treatment. The success of outpatient LMWH treatment will depend on close communication among all involved health care professionals with the help of a coordinator, along with adequate training of providers and patients receiving LMWH therapy.

### Summary

Outpatient treatment of DVT with LMWHs offers the opportunity to dramatically reduce the cost of treating DVT and improve the quality of life without compromising clinical outcomes. Given the choice, most patients are willing to be treated at home and are comfortable with or willing to accept the idea of giving themselves injections of LMWHs. Establishing comprehensive outpatient treatment guidelines is important to ensure that adequate support is provided by the anticoagulation provider. Pharmacists have assumed lead roles in developing and maintaining successful outpatient DVT treatment programs. Because of the safety, effectiveness, and potential savings associated with treating patients with acute DVT in the outpatient setting, ASHP encourages health care professionals to become or remain actively involved in the development and documentation of innovative outpatient DVT treatment programs. These programs will also facilitate the use of newer antithrombotic agents as they become available and receive approval for outpatient DVT treatment.<sup>10,26</sup>

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