ABSTRACT

There are more than 170,000 hospital admissions each year for deep vein thrombosis (DVT) in the United States. Moreover, there are approximately 90,000 readmissions for recurrent venous thromboembolic events, with an average length of hospital stay between 5 days and 7 days. This article reviews the clinical evidence related to inpatient and outpatient treatment options and their efficacies in achieving therapeutic goals for the clinical management of DVT. It also reports the medical evidence relating to eligibility criteria and dosing, as well as the American College of Chest Physicians recommendations regarding duration of therapy.

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Deep vein thrombosis (DVT) is a pervasive health problem, affecting 2 million people in the United States annually. As many as 60,000 deaths are caused by pulmonary embolism (PE) every year. As many as 600,000 pulmonary emboli will occur with approximately 60,000 deaths from these thrombotic events. Secondary complications such as postphlebitic syndrome and pulmonary hypertension contribute significantly to long-term morbidity and mortality in this patient population. While the death toll is tragic, the financial burden is significant; the cost of care for patients with DVT is an estimated $1.5 billion annually.

Clinical evidence documents the prevalence of undetected PE in patients with acute DVT. In a study of 622 patients with acute DVT but without PE, Meignan et al reported that radionuclide lung scanning revealed abnormalities in 82% of the patients; PE was thought to be present in 40% to 50% of the patients. These findings have strong implications for the clinical management of DVT, with the goals of preventing thrombus extension, thrombus embolization, early and late thrombus recurrence, and possibly postthrombotic syndrome (although clinical evidence in this last area is inconclusive).

Prompt administration of anticoagulant therapy is essential to preventing clot propagation and pulmonary emboli. Clinical evidence suggests that if patients achieve a therapeutic activated partial thromboplastin time quickly with heparin, the less recurrent disease occurs subsequently.

Figure 1 illustrates the efficacy of various approaches to DVT clinical management in accomplishing treatment goals, according to the current medical literature. In the United States, many physicians are placing inferior vena cava filters in patients who have extensive thrombosis in the deep femoral system up to the iliacs, in addition to administering anticoagulation therapies. However, using inferior vena cava filters in such circumstances in advance has not been supported.
by the medical literature. In terms of anticoagulation therapies, both heparin and low-molecular-weight heparin (LMWH) have proven effective in preventing embolization and extension as well as reducing recurrence. Hypothetically, LMWH and heparin may also prevent postthrombotic syndrome. LMWH may restore patency, but at this time insufficient clinical evidence exists to confirm these suppositions. Thrombolysis has proven effective in achieving 4 of the 5 treatment goals, but the extent to which it prevents embolization is questionable at this point. Following is a review of the clinical evidence related to the treatment options and their efficacies in achieving therapeutic goals for the clinical management of DVT. Excluded from the following trials were patients with hereditary or acquired coagulation disorders, creatinine clearance less than 30 cc/min, pregnancy, or cancer and unspecified concomitant chemotherapy.

**Enoxaparin versus Unfractionated Heparin**

A report by Simonneau et al shows that thromboembolic disease recurred in 1.5% (N = 67) of patients in an enoxaparin treatment arm, compared to 10.4% (N = 67) of subjects in the heparin group. In a study, de Valk et al compared the efficacy and safety of 2 subcutaneous doses of danaparoid, a long-acting agent, with that of continuous intravenous administration of unfractionated heparin (UFH) in the treatment of 209 patients believed to have venous thromboembolism (VTE). Patients were randomly assigned to either low-dose danaparoid (intravenous loading dose of 1250 U followed by 1250 U administered subcutaneously twice daily [N = 63]); high-dose danaparoid (intravenous loading dose of 2000 U followed by 2000 U administered subcutaneously twice daily [N = 63]); or UFH (intravenous loading dose of 2500 U followed by dose-adjusted continuous infusion [N = 60]). Treatment lasted at least 5 days. A significant reduction in recurrence or extension of VTE was seen in patients receiving high-dose danaparoid (8 of 63 [13%]), as compared with patients receiving intravenous UFH (17 of 60 [28%]); relative risk was 0.45 [0.21 to 0.96 (95% confidence interval [CI])].

Additional evidence suggesting that LMWH therapy results in fewer recurrences of DVT and PE has been reported by Hull in the *New England Journal of Medicine*. This double-blind clinical trial compared fixed-dose subcutaneous LMWH (tinzaparin), once daily with adjusted-dose intravenous heparin, given by continuous infusion for the initial treatment of patients with proximal-vein thrombosis. Six of 213 patients who received tinzaparin 175 units/kg (2.8%) and 15 of 219 patients who received intravenous heparin (6.9%) experienced new episodes of VTE (P = .07). Major bleeding associated with initial therapy occurred in 1 patient receiving tinzaparin (0.5%) and in 11 patients receiving intravenous heparin (5.0%), showing a reduction in risk of 91% (P = .006). However, this apparent protection against major bleeding was lost during long-term therapy. Another clinical trial comparing reviparin with UFH showed no statistically signifi-

**Figure 1: Therapeutic Goals and Treatment Options for DVT**

<table>
<thead>
<tr>
<th>Goals of therapy</th>
<th>Supportive care</th>
<th>IVC filter</th>
<th>Heparin</th>
<th>LMWH</th>
<th>Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent embolization</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Prevent extension</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Reduce recurrence</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Restore patency</td>
<td>?</td>
<td>?</td>
<td>★</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Prevent postthrombotic syndrome</td>
<td>?</td>
<td>?</td>
<td>★</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; IVC = inferior vena cava; LMWH = low-molecular-weight heparin.
A landmark study by Levine et al in 1996 evaluated the safety and efficacy of enoxaparin administered to outpatients. Patients with acute proximal DVT were randomly assigned to receive either intravenous standard heparin in the hospital (253 patients) or LMWH (247 patients received 1 mg of enoxaparin per kilogram of body weight subcutaneously twice daily) administered primarily at home. The study design allowed outpatients taking LMWH to go home immediately and hospitalized patients taking LMWH to be discharged early. All the patients received warfarin starting on the second day. Of the 247 patients receiving LMWH, 13 (5.3%) had recurrent thromboembolism, as compared with 17 (6.7%, 95% CI) of the 253 patients receiving standard heparin. Five patients (2%) receiving LMWH had major bleeding, as compared with 3 patients (1.2%) receiving standard heparin. In a separate study reported simultaneously, Koopman et al also demonstrated the safety and efficacy of outpatient administration of LMWH. Patients were randomly assigned to 1 of 2 study arms: adjusted-dose intravenous standard heparin administered in the hospital (198 patients), or fixed-dose subcutaneous LMWH administered at home (202 patients). Seventeen (8.6%) of the 198 patients who received standard heparin and 14 (6.9%) of the 202 patients who received LMWH experienced recurrent thromboembolism (95% CI). Major bleeding occurred in 4 patients (2.0%) assigned to standard heparin and in 1 patient (0.5%, 95% CI) assigned to low-molecular-weight heparin, as shown in Table 2. However, despite such convincing clinical evidence, many physicians in the United States are not using LMWH to treat patients with thromboembolic disease.

Table 3 shows findings from 3 separate meta-analyses of safety and efficacy of LMWH, as compared with UFH. Outcomes for recurrent VTE, major bleed, and mortality were consistently better for LMWH, as compared to UFH. Once-a-day administration was compared to twice-a-day dosing of LMWH and UFH in a randomized controlled trial of patients with proximal and distal clots. Investigators found that once-a-day dosing with enoxaparin 1.5 mg/kg was equally as safe and efficacious as 1 mg/kg q 12h and constant infusion IV of heparin; in both regimens, safety and efficacy were comparable to that of standard heparin therapy.

While most of the medical evidence regarding the safety and efficacy of LMWH focuses on the treatment of DVT, only limited data are available on the use of LMWH to treat acute symptomatic PE.
This subgroup of patients was selected for analysis in a random controlled trial of 612 patients with symptomatic PE who did not require thrombolytic therapy or embolectomy. Patients were randomly assigned to either SC LMWH (tinzaparin) once daily, or IV UFH. In the first 8 days of treatment, 2.9% of 308 patients assigned to receive UFH reached at least 1 of the endpoints, as compared with 3.0% of 304 patients assigned to LMWH (95% CI). By day 90 of the study, 7.1% of patients assigned to UFH and 5.9% of patients assigned to LMWH had reached at least 1 of the following endpoints: death, recurrent thromboembolism, or major bleed (P = .54). However, the risk of major bleeding was similar in the 2 treatment groups throughout the study. These findings suggest that initial treatment of PE with LMWH is at least as safe and effective as is treatment with UFH.

Looking at randomized trials of dalteparin, another formulation of LMWH currently in use, studies by Lindmarker et al, Fiessinger et al, and Luomanmaki et al found no significant differences between dalteparin and UFH for the variables of morbidity, PE/DVT, major bleeding, or thrombocytopenia.

In conclusion, a composite of all relevant study findings suggests that LMWH outcomes for recurrent thromboembolic disease and major bleeding are superior to those for UFH (Figure 2). Yet within the United States healthcare system, UFH is used more widely than is LMWH, largely due to lack of protocol development for outpatient care with LMWH.

**Criteria for Selecting Patients for Outpatient Anticoagulation Therapy**

Figure 3 offers a graphic illustration of combined clinical evidence regarding the incidence of major bleeding and recurrent thromboembolism in patients who are given UFH and in patients who receive LMWH. Based upon these study findings and their exclusion criteria, the following should be

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**Table 3. Meta Analyses of LMWH vs IV UFH DVT Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Leizorovicz et al</th>
<th>Lensing et al</th>
<th>Siragusa et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 d–23 mo follow-up</td>
<td>3–6 mo follow-up</td>
<td>90 d follow-up</td>
</tr>
<tr>
<td>VTE recurrence</td>
<td>n = 2045</td>
<td>n = 1086</td>
<td>n = 1228</td>
</tr>
<tr>
<td>RR</td>
<td>2.82% vs 4.63%</td>
<td>3.1% vs 6.6%</td>
<td>2.5% vs 4.5%</td>
</tr>
<tr>
<td>P</td>
<td>.09</td>
<td>&lt;.01</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Major bleed</td>
<td>n = 2045</td>
<td>n = 1512</td>
<td>n = 1694</td>
</tr>
<tr>
<td>RR</td>
<td>2.43% vs 4.04%</td>
<td>0.8% vs 2.8%</td>
<td>2.2% vs 4.7%</td>
</tr>
<tr>
<td>P</td>
<td>.15</td>
<td>&lt;.005</td>
<td>.04</td>
</tr>
<tr>
<td>Mortality</td>
<td>n = 2045</td>
<td>n = 1086</td>
<td>n = 1733</td>
</tr>
<tr>
<td>RR</td>
<td>3.30% vs 4.83%</td>
<td>3.9% vs 7.1%</td>
<td>3.3% vs 5.9%</td>
</tr>
<tr>
<td>P</td>
<td>.16</td>
<td>&lt;.04</td>
<td>.01</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; DVT = deep vein thrombosis; VTE = venous thromboembolism; RR = relative risk.

**Figure 2. Clinical Efficacy: LMWH vs UFH Venous Thromboembolism**

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**Figure 3. Criteria for Selecting Patients for Outpatient Anticoagulation Therapy**

Venous thromboembolism  
Pulmonary embolism  
Major bleeding  
Minor bleeding  
Total mortality  
Thrombocytopenia  

0.0 0.25 0.5 0.75 1 1.25 1.5 1.75 2  
In favor of LMWH  
In favor of UFH  
Pooled Relative Risk  

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin. Reprinted with permission from reference 22.
considered as absolute contraindications for outpatient treatment with LMWH:

- Active bleeding
- Cardiopulmonary instability
- Hereditary bleeding disorders
- History of heparin induced thrombocytopenia
- Allergy to heparin.

Social and medical relative contraindications for outpatient treatment with LMWH include the following:

- Geographic inaccessibility
- Potential for medication noncompliance
- Inability to support cost of drug
- Pregnancy
- Hereditary or acquired thrombotic disorders
- Peptic ulcer disease, gastrointestinal, or genitourinary bleeding within 6 weeks
- Uncompensated comorbidities
- Concomitant medical problems (eg, CrCl < 30 cc/min)
- Pulmonary embolism (hemodynamically stable). This was placed under the relative risk category because many US physicians are not clinically comfortable with treating patients with uncomplicated PE on an outpatient basis.

Koopman et al\textsuperscript{11} reported that 69% of the patients were eligible for outpatient treatment of DVT; Levine et al\textsuperscript{10} and Yusen et al\textsuperscript{18} respectively reported that only 33% and 18% of the subjects met the criteria to be treated at home. Within our facility at Thomas Jefferson University, we find that approximately 45% of patients meet eligibility criteria for outpatient anticoagulation therapy.

**Dosing Regimens**

Whether to administer once- or twice-a-day dosing of therapy remains controversial. Table 4 summarizes the incidence of major bleeding and recurrent DVT under various dosing regimens, but it is important to stress that these studies did not exclude patients on the basis of weight. However, in studies where dosing was fixed and not adjusted on actual body weight, outcomes for primary endpoints were less favorable (Table 5). In our study of once- versus twice-daily dosing

<table>
<thead>
<tr>
<th>Author</th>
<th>WT</th>
<th>Major Bleed</th>
<th>RVTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simonneau\textsuperscript{5} (enoxaparin)</td>
<td>No limit</td>
<td>0</td>
<td>1/67 (1%) q12h</td>
</tr>
<tr>
<td>Hull\textsuperscript{8} (tinzaparin)</td>
<td>No limit</td>
<td>0.5%</td>
<td>6/213 (3%) qd</td>
</tr>
<tr>
<td>Levine\textsuperscript{10} (enoxaparin)</td>
<td>No limit</td>
<td>2%</td>
<td>13/247 (5.3%) q12h</td>
</tr>
</tbody>
</table>

RVTE = recurrent venous thromboembolism.
with enoxaparin in which no weight limits were placed upon subjects, we found no significant difference in the outcomes of recurrent VTED or major bleeding within the qd and q12h study arms. However, in a subgroup analysis there was a higher incidence of recurrent VTED in obese patients and in patients with cancer who received qd dosing than for those patients who received q12h dosing, but the variance was not statistically significant. Nonetheless, it does raise some questions surrounding dosing, which again surface in reports from Partsch et al. This study of the safety and efficacy of dalteparin showed 5.3% (N=67) of subjects within the qd (200 units/kg) study arm experienced major bleeds and 5.3% experienced recurrent PE. In the 12 h D (100 units/kg) study arm, 1.5% (N=64) experienced major bleeds and 1.6% experienced recurrent PE.

Protocol for outpatient anticoagulation therapy at Thomas Jefferson University is based on recommendations from the American College of Chest Physicians (ACCP) consensus conference. The ACCP recommendations, as detailed in Table 6, call for administration of warfarin initiated on day 1 or day 2 with continuation of LMWH for at least 5 days, until an international normalized ratio (INR) value of 2 to 3 is achieved for 2 consecutive days.

In summary, UFH has long been the mainstay of therapy for DVT and PE. However, over the last 10 years, LMWHs have been replacing this therapy for treating thrombotic events. LMWHs are better absorbed, have a longer half-life, and do not require monitoring. A number of studies have demonstrated the safety and efficacy of LMWHs in treating patients with thromboembolic events. LMWHs have changed the paradigm of care for thromboembolic disease: outpatient treatment or shorter hospital stay for inpatients.

### Table 5. Once- vs Twice-Daily Dosing

<table>
<thead>
<tr>
<th>Author</th>
<th>W T</th>
<th>Major Bleed</th>
<th>RVTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koopman</td>
<td>Fixed dose</td>
<td>0.5%</td>
<td>14/202 (6.9%) q12h</td>
</tr>
<tr>
<td></td>
<td>(nadroparin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindmarker</td>
<td>Fixed dose</td>
<td>0%</td>
<td>11/91 (12%) qd</td>
</tr>
<tr>
<td></td>
<td>(dalteparin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Valk</td>
<td>Fixed dose</td>
<td>1%</td>
<td>8/63 (13%) q12h</td>
</tr>
<tr>
<td></td>
<td>(danaparoid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbus</td>
<td>Fixed dose</td>
<td>1.9%</td>
<td>27/510 (5.3%) q12h</td>
</tr>
<tr>
<td></td>
<td>(reviparin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RVTE** = recurrent venous thromboembolism.

### Table 6. ACCP Duration of Therapy

- 3 to 6 months
  - First event with reversible or time-limited risk factor
- > 6 months
  - Idiopathic VTE, first event
- 12 months to lifetime
  - First event with
    - Cancer until resolved
    - Anticardiolipin antibody
    - Antithrombin deficiency
  - Recurrent event, idiopathic or with thrombophilia

Data adapted with permission from reference 26.

### REFERENCES


