

Treatment of Deep Vein Thrombosis Using Low-Molecular-Weight Heparins

Based on a presentation by James B. Groce III, PharmD, CACP

Presentation Summary

Because it eliminates the need for intravenous infusions and lengthy hospitalizations, use of low-molecular-weight heparins (LMWHs) for the treatment of deep vein thrombosis (DVT) can improve patient outcomes of safety and efficacy and reduce the cost of medical care. In a meta-analysis of randomized controlled trials involving more than 3500 patients, treatment with LMWH versus unfractionated heparin was associated with lower mortality, a lower incidence of major bleeding episodes and thrombocytopenia, and an overall reduction of about 30% in morbidity from recurrent thromboembolism and bleeding. The meta-analysis also demonstrated cost savings of \$1900 per patient for those treated with LMWH. More recent studies evaluating several LMWHs in both hospital and outpatient settings have shown that the drugs are more effective in reducing risk for recurrent events and complications than unfractionated heparin. The use of LMWHs for outpatient treatment of DVT has, of necessity, given rise to specific protocols, inclusion and exclusion criteria, follow-up procedures, and multidisciplinary approaches to outpatient management. These guidelines are reviewed here, as are special considerations for patients who are obese or who have renal insufficiency.

Reducing medical care costs, especially the costs of drug therapy, without sacrificing patient outcomes of safety and efficacy is a major challenge for all healthcare systems. One therapeutic area in which this challenge can be met is the use of low-molecular-weight heparin (LMWH) in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism.

DVT affects 2 million people in the United States. Approximately 800,000 of them have postphlebotic syndrome, about 600,000 have PE, and 1 million have silent PE. Of those with PE, approximately 10% die and 5% develop pulmonary hypertension. The cost of treating these patients with venous thromboembolic disorders is estimated to be \$1.5 billion annually.¹

Unfractionated Heparin Versus LMWH

Traditional treatment of DVT with or without PE is carried out in the hospital and consists of an intravenous (IV) bolus of unfractionated heparin followed by continuous infusion for several days and the concomitant administration of warfarin initiated within the first 24 hours after the heparin bolus. Once heparin has been started, the activated partial thromboplastin time (aPTT) is monitored and the platelet count is checked daily. After at least 4 to 5 days of combined heparin and warfarin therapy and the international normalized ratio (INR) has been > 2.0 for at least 2 consecutive days, heparin therapy is discontinued. Warfarin therapy, with an adjustment of the daily dose based on the INR, is continued for at least 90 days at an INR of 2.0 to 3.0.

However, a review of the literature reveals that this treatment regimen is often subtherapeutic at 24 and 48 hours in many patients, despite unfractionated heparin dosing nomograms based on the patient's weight. This is particularly troublesome because the longer the patient remains on subtherapeutic therapy with

regard to the aPTT at the initiation of heparin, the greater the likelihood of thromboembolic disease recurrence. In some cases, subtherapeutic treatment, as indicated by the aPTT, can be explained by problems inherent to unfractionated heparin. Additionally, warfarin therapy is not initiated within the first 24 hours after the start of unfractionated heparin therapy, and sometimes delayed until 2 or even 3 days have elapsed; this leads to a prolonged overlap of concomitant heparin and warfarin therapies and an unnecessary increase in the length of hospital stay.

Several very important questions are raised by treatment with unfractionated heparin/warfarin:

- Would the use of LMWHs reduce the percentage of patients in whom treatment is subtherapeutic?
- Would the use of LMWHs reduce recurrent DVT?
- Would the use of LMWHs reduce the incidence of complications associated with anticoagulant therapy?
- Would the use of LMWHs, some of which have been approved for outpatient treatment of DVT, reduce the cost of care?

To answer these questions, it is first necessary to examine the differences between unfractionated heparin and LMWH, as outlined in **Table 1**. An important consideration is the preferential binding affinity of LMWH to factor anti-Xa relative to factor IIa or thrombin, which has improved the outcomes seen for the role of LMWH. Tissue factor pathway inhibition and suppression of von Willebrand's factor are also important, particularly in acute coronary syndromes.

Table 1 also summarizes the reasons postulated to explain the improved outcomes seen with LMWHs, including lack of binding to plasma proteins, macrophages, and endothelium; no increase in vascular permeability; and inhibition of platelet aggregation or no platelet/fibrinogen binding. The lack of binding to the endothelium and the lack of increased vascular permeability seen with LMWHs have been

suggested as a means of reducing the likelihood of hemorrhagic complications.

The degree of bioavailability after a subcutaneous injection is an important factor, both in terms of clinical outcome and pharmacoeconomics. As a class, the LMWHs have a bioavailability of about 90%, compared with 30% for unfractionated heparin. As noted in the Prophylaxis in Medical Patients with Enoxaparin (MED-ENOX) trial, which evaluated the safety and efficacy of the LMWH enoxaparin [see presentations by Dr. Tapson and Dr. de Lissovoy in this supplement] in acutely ill patients in the intensive care setting, many of these patients are hypoperfused. The combination of hypoperfusion and the low percentage of bioavailability seen with unfractionated heparin makes the drug inappropriate for acutely ill patients who simply cannot absorb it.

Table 1. Differences Between Unfractionated Heparin and Low-Molecular-Weight Heparin

	Unfractionated Heparin	Low-Molecular-Weight Heparin
Molecular weight (daltons)	12,000-15,000	< 5000
Targeted clotting factors	Thrombin, IXa, Xa, XIa	Xa
Xa:thrombin binding affinity ratio	1:1	3:1
AT III dependent	Yes	Yes
Inactivates clot-bound thrombin and factor VII	No	No
Binds to plasma proteins	Yes	No
Binds to macrophages	Yes	No
Binds to endothelium	Yes	No
Increases vascular permeability	Yes	No
Platelet aggregate effect	+++	+
Inhibits platelet:fibrinogen binding	Yes	No
Bioavailability after subcutaneous injection	30%	90%
Thrombocytopenia	++	+
Fibrinolytic activity	+	±
Half-life	1-2 hours	2-4 hours (peak 4-6 hours)

AT = antithrombin.

Also important to improved outcomes with LMWH are its lower molecular weight, its longer half-life, and the reduced likelihood of thrombocytopenia when compared with unfractionated heparin.

The overall benefits of LMWHs in comparison with standard unfractionated heparin have been shown in a meta-analysis of randomized, controlled trials involving 3566 patients with acute DVT (Table 2). In addition to significant reductions in the rates of mortality, major bleeding episodes, and thrombocytopenia, the use of LMWH was associated with an overall rate reduction of about 30% in mortality from recurrent thromboembolism, bleeding, and cancer. The meta-analysis also included a cost-effectiveness analysis of outpatient treatment of DVT, which showed a cost savings of \$1900 per patient among those treated with LMWH.²

Differentiation of LMWHs

Several LMWHs have been or are being studied, including nadroparin, dalteparin, reviparin, ardeparin, tinzaparin, and enoxaparin. Of these, enoxaparin is approved in the United States for inpatient treatment of DVT/PE and outpatient treatment of DVT; tinzaparin was approved for treatment of DVT with or without PE in the United States after study in hospitalized patients; and dalteparin is not yet approved for DVT treatment in this country but is being studied in clinical settings.

As shown in Table 3, the LMWHs differ slightly from each other as well as differing considerably from unfractionated heparin. Differences in molecular weight,

bioavailability, half-life, anti-Xa to anti-IIa binding affinity ratios, and peak anti-Xa activity account for differences in dosing and outcomes.³

Current Treatment Approaches with LMWHs

The current guidelines for the use of LMWHs in the treatment of DVT with or without PE were released earlier this year by the American College of Chest Physicians (ACCP).⁴ Once treatment with an LMWH—either enoxaparin, tinzaparin, or dalteparin at the doses outlined below—is initiated, an appropriate dose of warfarin should be started on day 1, with dose adjustments as needed. Therapy with LMWH should be stopped after at least 5 days of combined therapy with LMWH and warfarin when the INR is > 2.0 for 2 consecutive days. A complete blood count, a stool occult blood test, and a platelet count should be done between days 3 and 5.

Enoxaparin is given as a subcutaneous injection at a dose of 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours. Tinzaparin is given as a once-daily subcutaneous injection at a dose of 175 anti-Xa IU/kg/day. Dalteparin is given as a once-daily subcutaneous injection at a dose of 200 anti-Xa IU/kg/day, with no single dose exceeding 18,000 IU.^{4*}

Studies have found that efficacy of dalteparin is decreased, both in comparison with unfractionated heparin and with other LMWHs. The reason for this is most likely the “capped” dose of 18,000 IU, which would suffice for patients weighing up to 90 kg, but apparently not for those weighing more than 90 kg. For example, in 4 studies evaluating dalteparin (and finding decreased efficacy), patients weighed as much as 117 kg,⁵ 128 kg,⁶ 113 kg,⁷ and 146 kg,⁸ although the dosing weight was “capped” at 90 kg or 18,000 IU.

Reduced efficacy of dalteparin was also noted in 2 review articles comparing the mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety of

Table 2. Benefits of Treatment with Low-Molecular-Weight Heparins Versus Unfractionated Heparin

Outcome Variable	Low-Molecular-Weight Heparin	Unfractionated Heparin	P Value
Mortality	5.1%	6.7%	.02
Major bleeding	1.2%	1.9%	.05
Thrombocytopenia	1.2%	1.8%	.05

Source: Reference 2.

*Unlabeled/unapproved use of drug.

unfractionated heparin and LMWHs. In those reviews, 16 of 322 patients (5%) treated with dalteparin had recurrent DVT within 30 to 60 days after initiation of therapy compared with 8 of 339 patients (2.4%) treated with unfractionated heparin. In contrast, 6 of 213 patients (2.8%) treated with tinzaparin had recurrent DVT in 30 to 60 days compared with 15 of 219 patients (6.9%) treated with unfractionated heparin; 13 of 314 patients (4.1%) treated with enoxaparin had recurrent DVT in 30 to 60 days compared with 20 of 320 patients (6.3%) receiving unfractionated heparin.^{9,10} The potential for rehospitalization for the same diagnosis (DVT) within 30 days has important economic implications in the United States because it requires that the patient be treated within the dollar amount initially allotted by Medicare for the original diagnosis-related group (DRG).

Once-daily versus twice-daily dosing has been studied, not only to see what effect the dosing schedule has on efficacy and safety, but also as a potential means of reducing the cost of drug therapy. One study evaluating once-daily tinzaparin (with no weight limit) in patients with PE¹¹ and another evaluating once-daily and twice-daily enoxaparin (also with no weight limit) in patients with DVT/PE¹² found that the rates of DVT recurrence and major bleeding episodes were comparable. Another study evaluating once-daily and twice-daily dalteparin (with no weight limit) in patients with DVT¹³ found that rates of recurrent DVT and major bleeding episodes were considerably lower with twice-daily dosing (1.5% and 1.6%, respectively) than with once-daily dosing (5.3% for both).

The study comparing once-daily enoxaparin with twice-daily enoxaparin with unfractionated heparin in the inpatient setting found no statistically significant differences in DVT recurrence or hemorrhagic complication rates among the 3 treatment arms.¹² Data on medical resources use from the US patients in this study were used to compare costs for DVT patients treated with once-daily enoxaparin (n = 112), twice-daily enoxaparin (n = 123), or unfractionated heparin (n = 104)

in a cost-minimization study designed to reflect the perspective of a third-party payer.¹⁴ Data were collected to reflect resources used during the initial in-hospital treatment and during a 3-month follow-up period, including long-term oral anticoagulation therapy and hospital readmissions.

The initial length of stay was similar for all 3 treatment groups, but patients treated with unfractionated heparin were more likely to be rehospitalized within the 3-month follow-up period for any reason and for DVT recurrence than were those receiving either dose of enoxaparin (Table 4). Total costs over the 3-month period for hospitalization, laboratory work, physi-

Table 3. Differentiation of 3 Low-Molecular-Weight Heparins Versus Unfractionated Heparin

Variable	Unfractionated Heparin	Enoxaparin	Dalteparin	Tinzaparin
Bioavailability	20%	91%	87%	90%
Half-life	~ 1 hour	4.5 hours	3-5 hours	1.5 hours
Molecular weight	~ 15 kd	4.2 kd	6 kd	4.5 kd
anti-Xa, anti-IIa	1.0	3.8	2.7	1.9
Peak anti-Xa	4-6 hours	3-5 hours	3-4 hours	4-6 hours

Source: Reference 3.

Table 4. Use of Medical Resources 3 Months After Initial Hospitalization for Treatment of Deep Vein Thrombosis

	Unfractionated Heparin	Enoxaparin (Once daily)	Enoxaparin (Twice daily)
Number of patients (United States)	104	112	123
Initial length of stay (mean)	8.2 days	8.5 days	8.2 days
Any rehospitalization	26%	20.5%	17.1%
Rehospitalization for venous thromboembolic disease	17.3%	10.7%	8.9%

Source: Reference 14.

cians' fees, and medications were similar in the 3 treatment groups. The additional cost of enoxaparin was offset by fewer hospital readmissions and shorter readmission lengths of stay. Importantly, the potential cost savings of once-daily dosing with enoxaparin compared with twice-daily dosing was found to be \$385 per treatment course.¹⁴

Outpatient Treatment

Three trials involving patients with DVT without PE compared outpatient treatment with LMWH and in-hospital treatment with unfractionated heparin. No statistically significant differences were found in DVT recurrence, bleeding events, and death. The only statistically significant difference was the reduced length of hospital stay in the outpatient group.¹⁵⁻¹⁷ In 1 of these studies, in fact, 53% of the 247 patients receiving enoxaparin were discharged from the vascular laboratory the very same day DVT outpatient treatment was initiated.¹⁶

Outpatient management of DVT with LMWH requires a multidisciplinary team of emergency department, inpatient, and outpatient physicians; pharmacists; social workers; patient educators; and possibly home nurses, although their services are being used less as patients become accustomed to self-injection of LMWH. A systematic approach in which these professionals work together to manage DVT on an outpatient basis has been suggested by Dunn and Coller.¹⁸ In this approach, the communication between the home nurse and outpatient physician regarding the patient's symptoms, INR, warfarin dose, and possible need for follow-up care is especially important.

Although inclusion criteria for outpatient treatment of DVT may vary somewhat by institution, candidates should minimally meet the following requirements:

- Proximal DVT or symptomatic distal DVT
- At least 18 years of age
- Medical and hemodynamic stability
- Willingness and ability to be sent

home from the clinic or emergency department

Variability is most likely to be seen with regard to the fourth criterion, with some experts willing to discharge very few patients to early home care, whereas others opt for early discharge for the overwhelming majority of their patients.

Relative exclusion criteria are as follows:

- Iliofemoral DVT
- Phlegmasia
- Symptomatic PE
- Pregnancy or childbearing potential without contraception
- Gastrointestinal bleeding in the previous 10 days
- Positive stool guaiac
- History of a bleeding disorder
- Major surgery/trauma or stroke within the previous 2 weeks
- Need for aspirin or nonsteroidal anti-inflammatory drugs
- History of heparin-induced thrombocytopenia
- Severe renal dysfunction
- Morbid obesity
- High potential for noncompliance with therapy

Treating DVT in a patient with renal insufficiency requires an increased dosing interval or a decreased daily dose to avoid the accumulation of a renally cleared drug. The half-life of LMWH is prolonged in patients with renal insufficiency, and a potential increase in bleeding complications can occur in patients with serum creatinine levels above 2.0 mg/dL. For these reasons, increasing the dosing interval to once every 24 hours makes sense, using a dose of 1.5 mg/kg* as shown in the study of Merli et al that evaluated enoxaparin.¹² For patients whose creatinine clearance levels are below 30 mL/min, unfractionated heparin may be appropriate or if an LMWH is used, anti-Xa monitoring is suggested.

LMWH dosing in obese patients has not been specifically addressed in clinical

*Unlabeled/unapproved use of drug.

studies, and limited clinical information is available. In controlled trials using weight-adjusted dosing, the LMWH doses used were based on actual body weight, with 158.6 kg being the maximum weight reported. At this point, adjusted doses or capped doses are not recommended. For patients who weigh in excess of 160 kg, alternate measures of anticoagulation should be used. If, however, LMWHs are used, anti-Xa monitoring should be considered.

The outpatient DVT protocol with regard to medication prescriptions is an important element of hospital discharge. Patients should be discharged with prescriptions for a 5- to 7-day supply of subcutaneous enoxaparin 1 mg/kg every 12 hours, with the dose rounded upward. Additionally, a prescription for appropriately dosed warfarin is necessary. Dosing is a critical issue with warfarin as well, because an incorrect dose can adversely affect therapy with unfractionated heparin or LMWH. Warfarin doses are 5 mg/day for patients weighing less than 80 kg, 7.5 mg/day for patients weighing more than 80 kg, and 2.5 mg/day for patients who are frail, elderly, or malnourished.

Regarding follow-up, many outpatient DVT protocols require daily monitoring of prothrombin/INR, platelet count on days 3 and 7, daily telephone assessment by a nurse or pharmacist, and physician follow-up at 1 week and as needed.

ACCP Recommendations

Recommendations from the 6th ACCP Consensus Conference on Antithrombotic Therapy addressing effective regimens for the treatment of DVT acknowledge that unfractionated heparin, LMWH, and adjusted-dose subcutaneous heparin are effective for the acute treatment of DVT or PE and should be used for a minimum of 4 to 5 days. Although subcutaneous injections of unfractionated heparin have been found to be effective in grade 1A clinically controlled trials, this may not be the case in the “real world.”

In its recommendations, the ACCP also noted that LMWH, in comparison with unfractionated heparin, offers the major

benefits of convenient dosing and facilitation of outpatient treatment. Furthermore, LMWH may result in slightly less recurrent DVT and may offer a survival benefit in patients with cancer. On the basis of these findings, and on evidence from grade 2B clinical trials, the ACCP recommends that clinicians use LMWHs over unfractionated heparin for the treatment of DVT.

... DISCUSSION HIGHLIGHTS ...

Lower Incidence of Recurrent DVT

Dr. Perler: Does the lower incidence of recurrent DVT in patients who receive LMWH as opposed to unfractionated heparin reflect better, more rapid clot resolution during the acute event, or is there something else going on? Why did these patients have a better midterm outcome?

Dr. Groce: Some of the pharmacologic differences regarding LMWHs play themselves out into important clinical outcomes. We’re beginning to see important clinical differences with regard to patient outcomes.

In the Merli et al paper published in the *Annals of Internal Medicine* in February 2001,¹² when these patients were observed for 3 months after discharge from their index hospitalizations, we know that the problems with unfractionated heparin seemingly accounted for the increased readmission to the hospital, with an increased likelihood of recurrent DVT.

Dr. Thapar: I want to know if the aPTTs were checked in the people who had recurrences to see if they were in the range we needed. If you start patients on unfractionated heparin, with the regimen most of us use, one third of the patients have aPTTs in the range we need at the end of the first day, one third reach the range by the second day, and some go beyond that time. At least some studies have reported that.

Basically, you’re not achieving the end points that are required in the first few days, where it’s critical to stabilize the thrombus. I don’t know if the patients who were having recurrences fell into the ranges that were needed.

Dr. Groce: On that, I might rest my case regarding the role and utility of unfractionated heparin versus LMWH. Despite our best efforts to use weight-based dosing nomograms, we're having more and more problems achieving therapeutic effect. Even with a controlled clinical trial, your observation that the aPTT may not be in the range needed stands true, but outside of a controlled clinical trial, it may foretell even worse outcomes with respect to patients treated with unfractionated heparin.

In a healthcare system that does not have a weight-based dosing nomogram, where heparin is still empirically dosed at 1000 units per hour, we know we pay a price in terms of efficacy and safety outcomes.

In 1 trial in patients with acute coronary syndromes, the investigators examined aPTT outcomes and found that 93% of the patients treated with unfractionated heparin had a therapeutic aPTT.¹⁹ In some settings we do achieve therapeutic effect, and in some, quite frankly, we don't, and that's because of the pharmacologic problems with the drug.

Dr. Perler: I can tell you that on my service, in the real world, the single most important cause of problems in the medical management of patients is heparin anticoagulation. Forget venous disease, I'm just talking about patients undergoing reoperative distal bypass surgery where anticoagulation is really needed to give them every benefit. It is a constant push/pull: either they are overanticoagulated, or they are subtherapeutic. Despite excellent residents and attending physicians, it is a never-ending problem. It happens almost on a weekly basis, and frankly, leaves many of us not wanting to use heparin even where it really may benefit the patient. It is an ongoing, day-to-day, practical issue. My point is that there are potential benefits of LMWH in the inpatient setting for patients with arterial as well as venous disease.

Dr. Tapson: It makes sense clinically that there are lower recurrence rates on LMWH

over the ensuing months. There's no objective proof, but if you have drugs such as LMWHs that are more bioavailable than standard heparin, get to antithrombin 3 more specifically, and do not bind to acute phase reactants, macrophages, and other plasma proteins, they do the job more quickly. People with DVT have the potential for recurrence for the rest of their lives. Once you have valve damage in a vein, you're at risk for recurrence.

Dr. Perler: There is good duplex evidence showing that the more rapidly the clot resolves, the lower the incidence of post-phlebotic syndrome. That's been shown in numerous, well-documented, objective duplex studies. I think that's a viable hypothesis.

Dr. Michota: I think the problematic issues of achieving therapeutic levels on unfractionated heparin are very important. If I were to go to any hospital in the United States that is using any nomogram, I would find about 20% of patients who are not therapeutic, either over or under. So certainly, the ease of administration and the almost immediate anticoagulation at a therapeutic dose that you see with LMWH explain some of the outcomes.

Another interesting finding is the mortality advantage seen in patients treated with LMWH. Most of the LMWH trials that studied DVTs did not actually characterize whether or not those DVTs were idiopathic. Certainly, the data from the Gould et al² meta-analysis would suggest some other markers of future disease that we don't yet recognize. In most trials with a spectrum of patients, you're going to have people with occult malignancies and/or some other markers of future disease that we don't even understand. We may be seeing some differences with LMWH, albeit by mechanisms we don't completely understand, but they're leading to decreased recurrence rates. I would expect there are probably other effects of LMWH, which have not yet been characterized, that are going to be beneficial.

Dr. Tapson: That's also suggested in the

Dolovich et al²⁰ meta-analysis, in which the mortality rate was lower in the LMWH group, and it was not because of a reduction in venous thrombosis or thromboembolic events. It was because of something else.

Dr. White: Are there any other potential confounding factors or differences in disease severity or comorbidities that could be causing a higher recurrence rate in patients receiving unfractionated heparin?

Dr. Tapson: There are certainly limitations to meta-analyses in general. I think we're all aware of those. If you look at small numbers of events in large numbers of studies, sometimes you can make assumptions that may not be true. That may be 1 factor.

Generally speaking, a lot of these treatment and prophylaxis studies have been fairly well matched in terms of gender distribution and percentages of patients with cancer, previous DVT, etc. They generally compare pretty well, but other confounding factors certainly could be present.

We haven't yet done large enough studies with LMWH in the treatment realm to teach us everything we need to know. We need to do studies of 5000 or 10,000 patients or more, so we can really get a better idea of recurrence rates and mortality.

LMWH as First-Line Therapy

Dr. Perler: Do we now have sufficient data, both clinical and economic, to make a case that LMWH should be used as first-line treatment for a hospitalized patient with DVT?

Dr. Tapson: I think we do. In drafting the ACCP guidelines for *Chest*,⁴ there were some concerns about whether we should make that first-line recommendation specifically. If I were in the hospital, I would want to be treated with a once- or twice-daily subcutaneous injection, not an IV line that needs to be replaced. I would not want to have blood drawn every day; maybe every other day or every couple of days. If, however, I were at risk of bleeding, but still safe enough to be anticoagu-

lated, I might want to be on a drug that was out of my system in 4 hours. I might want to be on IV heparin. I think there is still a role, but we should be switching.

When we did the guidelines for *Chest*,⁴ there were several Europeans on the treatment section. They have used LMWHs for some time, and I sometimes think they are almost laughing at us for our persistence in using unfractionated heparin. We only emphasize that LMWHs are easier to use and make more sense apart from the situation where unfractionated heparin might be more appropriate.

Dr. Michota: In my personal practice as a hospitalist at the Cleveland Clinic Foundation, I use LMWH as a first-line drug. Other colleagues at my institution don't always do that. I don't know if it's because they are not familiar with LMWHs or because we have fairly well-scripted, weight-based heparin dosing nomograms on the order sheets that are used on our cardiac floors. There is, of course, a familiarity with the use of unfractionated heparin.

I definitely think the evidence for LMWH is there, and I beat the band at my institution as to why people are continuing to use unfractionated heparin.

Dr. Perler: At my institution, Johns Hopkins, it is cost. How have you made that case if you don't have the data to show the cost of the complications? The costs of hematomas my patients get don't get included in the pharmacy budget.

Dr. Michota: In working with the pharmacy and therapeutics committee, much of the information discussed is the same as we just saw here. When Cleveland Clinic physicians first presented the argument at my institution that tissue-plasminogen activator (t-PA) was better than other thrombolytic therapies, we noted that although t-PA was more expensive, it was a better quality drug that produced better outcomes and would be more cost effective in the long run. The same argument applies here. Yes, there are going to be more drug-acquisition costs up front, but

overall you're going to get better outcomes and that's a very persuasive argument.

There are different cost pressures, depending upon what system you're working in, but my institution prides itself on providing world-class care. Quality is balanced with cost. Any resistance to LMWH at my institution has not been related to cost, but a lack of awareness of the benefits that LMWH can provide.

Nursing Issues

Dr. Tapson: We run into nursing issues, and I'd be interested to know what the pharmacoeconomics experts on this panel think about this. We have a nursing shortage, especially on our pulmonary service. We have traveling nurses who don't know the floor and the patients. I don't know how to translate nursing time and effort into pharmacoeconomics, but our nurses certainly don't want to give standard heparin prophylaxis 3 times daily, or even twice daily if they can help it, and they don't want to deal with an IV heparin set-up where they have to hang the bag, recheck the bag, etc.

These things all take a tremendous amount of time, and time is money. I'm very interested in how you characterize those things. To me, if the nurse can do more than hang and recheck IV bags, he or she is saving time and probably money.

Dr. Michota: Another issue is preparing patients before going home, and this is much easier if the patient is on LMWH therapy. The educational process is much easier if we start off with LMWH from day 1. It also eases the transition to going home after 1 to 2 days.

Dr. de Lissovoy: I think Dr. Tapson hit on an important issue, something you have probably encountered in your institutions: the silo mentality. Formulary committees tend to look at the cost of heparin, not at the overall flow of resources needed to manage the patient. Shortages in nursing care, technicians, couriers to the laboratory, and everything else that is involved are costs we have not been able to measure because they require time and motion

studies, and we rarely do that. As a result I think we've estimated the potential savings in shifts of resources very conservatively.

Dr. White: We haven't done a lot with regard to nursing time and other resources consumed, but clearly all relevant costs need to be considered. Then we should assess the outcomes we are achieving for the costs we are paying to estimate cost effectiveness. The cost effectiveness of LMWH therapy for DVT prophylaxis can be compared with other viable treatment alternatives. We would select the therapy that would give us the most favorable outcome at the lowest possible cost.

Dr. Groce: I wholeheartedly agree with the comments, but I want to give you the counterargument I have heard so often by hospital administration, and then refute that. The hospital administrator will say it is the job of the nurse in the hospital to do all the things we're asking her or him to do with respect to unfractionated heparin, its intensive monitoring, the laboratory draws, etc.

In our particular setting, we can have those nurses doing their "job" and still attend to other patients because the only reason the patient with DVT is in the hospital is to have the DVT treated safely and effectively, which we can achieve outside of the hospital with the use of LMWH. It has now been demonstrated that this can be achieved safely and effectively with subcutaneous injections of LMWH.

If we instead divert the time and effort the bedside nurse expends in having to chase aPTTs and hang unfractionated heparin bags, and allow that nurse to care for other patients on the service, it becomes more cost effective. Early discharge from the hospital of the patient in DRG 131, which pays about \$4000 in our geographic locale, and use of that hospital bed for a patient in a higher-paying DRG who may be more in need of the nurse's skills is more cost effective for one's healthcare system.

The care that goes into managing a DVT patient isn't care for the patient per se. It's

being attentive to all of the problems associated with heparin: monitoring it effectively and making certain all documentation is accurate. Heparin has been cited as 1 of the 3 most litigated drugs documented in the literature, so recording that it is being appropriately administered in the hospital is crucial.

Dr. Thapar: I think you can sell this concept to an administrator once you show an increase in the patient-to-nurse ratio after you've switched to a subcutaneous LMWH program. For example, patients on IV heparin were staffed at a 6:1 ratio, but with subcutaneous LMWH, they're now staffed at 7:1 or 8:1. You also have to show that the switch from unfractionated heparin to LMWH offsets the increased drug cost, which the administrator sees as a fixed pharmacy and laboratory (P & L) cost.

Dr. Wales: In our location, nurses are not being paid based on a DRG, but at a per diem rate. Actually, that P & L line becomes very critical because, as Dr. Thapar pointed out, it's a fixed cost for that nurse. As soon as you go to a higher cost medication against a per diem rate, you are actually blowing your budget more significantly than you did before, and that really makes a big difference.

Dr. Tapson: It's also difficult to do a study like that. You'd want the nurses to be blinded to the fact that they are being studied. If I were faced with a study that might suggest I would be taking care of more patients, I would be moving slowly as I do those injections. You would have to be very careful about how you do the study.

Dr. Thapar: I agree.

Pharmacy Issues

Dr. Perler: The science of cost accounting in healthcare and in the hospital is very complex and very difficult. From my reading of it, and I am a novice, the first problem is the pharmacist's budget, which is now going to be 30% to 35% over budget every year. Then you say, "We want to use

this more expensive drug, but we'll free up some nursing time." That's a hard sell unless the pharmacist sees some downstream savings that are going to be reflected at the end of the year.

The other issue is the enormous number of medication errors in hospitals, and heparin is 1 of the prime drugs cited in lawsuits. I took a patient to the operating room a couple of years ago, who had asymmetric septal hypertrophy and had thrown a clot to the popliteal artery. He was on heparin, and he was bleeding. We found out after the fact that he received 25,000 units of unfractionated heparin in the hour before we took him to the operating room. This sort of thing happens not infrequently. Fortunately, the patient did fine, but these things happen with great frequency, they're documented nationally, and I think it is a crucial issue.

Dr. Witter: That's what helps in the argument to use LMWH. That's definitely 1 of the angles you can take, and say, "Hey, look, by giving this drug, which is so much less involved than unfractionated heparin, we can avoid some of these incidents."

Dr. Perler: There are other barriers. Just a year or so ago, I was called by an ad hoc pharmacy committee in our hospital whose members wanted to reintroduce streptokinase. We were using urokinase, and they said, "Wait a minute, streptokinase is so much cheaper. Why aren't we using streptokinase?" I said, "Well, we put that to bed many years ago. Urokinase is safer, more effective, and ultimately it's cheaper." But the pharmacists were—and are—under great pressure to control costs every way they can.

Dr. Michota: Yes, and that's why you always have to put in the value argument, or the value equation, which is quality over cost. It's not just about cost alone. Nobody here would buy a car without a steering wheel because it was the cheapest car out there. There has to be quality, and that's why some of these types of analyses are so difficult because it's hard to measure the value. It's easy to measure the cost,

but you have a lot of extrapolation to do when you start talking about quality. You have to factor in greater patient satisfaction, fewer recurrences, and fewer complications. How do you add these elements into your overall numbers? It is a very nebulous, very difficult process. When you start tying everything together, the LMWHs are, if nothing else, of higher quality, both in terms of their properties and how they're applied. However, to put that on a balance sheet next to the cost is not so easy. In terms of drug acquisition, you've got your work cut out for you to demonstrate the quality and maximize the value.

Dr. Tapson: It's not that we can't put more emphasis on patient satisfaction. There are data that are obvious and easy to accumulate showing that subcutaneous injections are much easier for patients than an IV line. They're not being awakened in the middle of the night for IV checks and they can ambulate more easily, which is beneficial. These are really direct patient care issues that should be explored and clearly linked to better patient satisfaction, better outcomes, shorter hospital stays, lower recurrence rates, and so on. Something like ambulation is an important issue in patient satisfaction, but we always tend to put it at the bottom of the list because it doesn't seem to be as crucial as cost.

Insurance Industry Perspective

Dr. Perler: I'm interested in the insurance industry's perspective on quality versus cost versus patient satisfaction. Dr. Hoffman, could you comment on that?

Dr. Hoffman: I think this is a no-brainer. When evaluating any drug you usually look at 3 things: efficacy, safety, and cost. Regarding efficacy, the evidence is clear that LMWH works, the results are more reliable, and it is easier to use than unfractionated heparin. Regarding safety, again it's a better drug. The meta-analyses showed significantly less mortality and bleeding. It has also been demonstrated that patients are more satisfied with

regard to treatment and quality-of-life issues. IVs are not needed, frequent blood draws are not necessary, and hospitalization can be avoided.

In terms of cost, there are clear-cut savings if hospitalizations can be avoided. Our plan, in the next few weeks, is about to roll out an initiative to treat DVT without complication on an outpatient basis. Three options are recognized. The first is to continue treating DVT on an inpatient basis. The second option is to use a short-stay unit in the hospital for 1 day to initiate treatment and then follow with 4 additional days at home. The third option is to treat the patient at home for the entire 5 days. It is anticipated that 50% of uncomplicated DVT patients can have their treatment begin in the physician's office and another 25% can be treated in a 24-hour short-stay unit where payment is for an observational level of care rather than a full DRG. The remaining 25% will require hospitalization. Our home care division has received permission to administer the first dose of enoxaparin. With almost all other drugs, because of the risk of reaction, a physician gives the first injection.

Our challenge in order to ensure this initiative's success is to educate the physician about the efficacy and safety of LMWH. Incentives can be added to get physician participation so everybody can win.

Dr. Perler: Another problem I have encountered is payment for the drug for patients who do not have a prescription drug plan. We often try to use LMWH to bridge patients who are on warfarin chronically and need to come in for an arteriogram or surgery. We don't want to admit them to the hospital for 3 or 4 days and put them on IV heparin, but if they are admitted and given heparin in the hospital, the insurance company will pay the bill if we can justify the hospitalization. However, if we don't admit them, but send them to the pharmacy with a prescription for LMWH and they don't have a prescription plan, that is a major problem. At least in our geographic area, it has

been very difficult to get the payers to pay for what is ultimately a cost savings and a more appropriate way to treat these patients.

Dr. Hoffman: In our plan the physician is not at risk for any drug costs. Enoxaparin is an injectable and is paid for under the pharmacy benefit. This implies a copay on the part of the patient. To encourage success of our initiative to treat DVT on an outpatient basis, enoxaparin, when used according to our guidelines, becomes a medical benefit eliminating any and all costs to the patient.

Dr. Thapar: In the California model and most likely nationwide, injectables generally are not covered under pharmacy benefit. This risk is usually shifted to the independent practice association or medical group under their health maintenance organization (HMO) contracts. Provider networks in California are receiving about \$40 per member per month (PMPM) for commercial patients. This imposes significant financial risk for physician groups who have to provide and manage their patients' healthcare needs and pay for injectables in California models.

Because of escalating costs of providing care for our patients, many provider groups in California are at the brink of financial crisis. I would hazard a guess to state that about 40% to 50% of the provider groups would not be meeting tangible net equity required by the Department of Managed Health Care.

In this uncertain and precarious environment we are being inundated by a plethora of new and expensive drugs. For the most part, these medications enhance management of our patients with better outcomes, however at the expense of diminishing revenues to the provider groups and further destabilizing their financial viability.

I believe we need to somehow have the employers and/or patients bear the cost of their care more than their current participation allows. We need to tell them, "We have these wonderful new drugs and technology to provide better care for you, but it

will cost \$10 PMPM more than what you are currently paying." I hope we can make healthcare consumers understand this dilemma and recruit their support for increased funding for healthcare.

In a capitated system such as managed care, provider groups receive fixed premiums PMPM on assigned enrollees from HMOs. This fixed premium serves to pay, for the most part, for physician services in addition to injectables. In recent years the cost of injectables has risen some 20% annually. This has caused the shift of payments from physician compensation to injectables and other newer expensive technologies. Unless we can address this problem and provide a reasonable solution, provider groups in California that assume risk for injectables, pharmacy, and chemotherapy will be hard pressed to survive and provider incomes will continue to decline.

Dr. Groce: You've addressed something that's very important, and that is we all have a different perspective regarding where we are geographically and our payer mix. We identified several years ago that it's just not enough to go to the third-party payers: you have to go to the people who write the contract with the third-party payer to cover their employees. We met with third-party payers in our area and agreed on contracts that would allow patients to come to our medical daycare unit and be treated and then discharged early from the hospital.

We have to keep expanding our contact with different parties, and include different payers, different providers, and people from the pharmaceutical industry so they will understand all these issues. For years, we've advocated that hospital administrators come to meetings like this so they would understand what the issues are, and why it's important to look beyond the drug therapy budget to the global impact of these decisions.

There is an initiative under way to examine thromboembolic disease and clarify the problems it poses to our healthcare system and its financial burden.

Barriers to Outpatient Treatment

Dr. Perler: What are the barriers to outpatient therapy?

Dr. Groce: At first, it was lack of physician acceptance, but that was overcome very quickly by the preponderance of evidence in the literature. Second was reimbursement, but we've made major headway on this issue, particularly in the Carolinas.

Logistical issues are the third barrier. We know it takes a healthcare professional to ready a candidate for outpatient LMWH therapy to go outside the hospital. The preparation includes patient education, demonstration of the first injection, and documentation that the patient has been instructed and the injection given. At that point, the case manager calls to make sure the third-party payer is going to pay for the drug.

Hospital administrators need to be reminded that before switching to the outpatient program, we would have spent 5 days or 120 hours with a score of healthcare providers having to lay eyes and hands on this patient to give care and time. Based on the reimbursement we have sought and have been given, the 2-hour visit by our pharmacist is one of the most cost-effective 2 hours in our hospital day.

Dr. Witter: What helps with gaining physician acceptance is the anticoagulation clinics springing up everywhere. In some, the physician and the pharmacist work together as a team. I think that's helping to get the word out that LMWH given on an outpatient basis is acceptable medical practice. Albuquerque has a well-established anticoagulation clinic with set protocols and it's really moving forward.

Dr. Tapson: Anytime physicians realize something will be taken care of if they can make just 1 telephone call, it's really appreciated.

Dr. Wales: Yes, but what you need to understand is that it's not just the 2 hours of the hospital case manager's time; it's another 24 hours on the outpatient case manager's side to do it, and it's 2

hours to set everything up and get everybody to agree it's going to be done on an outpatient basis, and then it takes somebody else to make sure all of those systems actually work once the patient is home.

I think what you're alluding to with the anticoagulation clinics is that there is an assurance for the physician that somebody is following through to make sure the home health agency actually goes out, the medication actually gets delivered, and the patient and/or caregiver actually understands what they're doing. There is a huge component on the outside that has to occur to make sure you've got a successful treatment on the outpatient side rather than just getting it started in the hospital and initiating a process of cost savings.

Dr. Tapson: That makes it even more acceptable to the physicians because they can make 1 telephone call and all this work gets done.

Dr. Hoffman: We're fortunate to have home care as a subsidiary of our plan. Cooperation is a given. I also would like to emphasize the need for only 1 telephone call (it is called Home Care Direct). Physicians want simplicity and efficiency. Home care is the lynchpin of this outpatient initiative and efficiency is necessary to make this program work. It starts with a single phone call. A nurse will then be available to begin treatment within 2 hours. The home care division is responsible for assessment, treatment, education, INR, fecal occult blood testing, and keeping the physician informed. I should also mention that the plan added a monetary incentive to the physician for taking the responsibility of managing the patient at home. A global fee has been established that is in excess of what the physician would get if the patient was hospitalized for 5 days. Just as in real estate it is location, location, location; with home care treatment of DVT it is logistics, logistics, logistics. Everything has to work smoothly but once accomplished there are significant rewards and savings for everyone.

Dr. Tapson: Although home healthcare is certainly necessary in some cases, it is not necessary in many. If you have responsible and compliant patients, they can learn how to inject themselves, go home, and never see anybody. They come back to the clinic, get an INR drawn—or in some cases, have it drawn and are checked at home—and come back to the physician for a checkup. It's very streamlined, and that's 1 of the critical issues: making sure that you make the appropriate decision regarding outpatient selection and utilizing home healthcare when it's needed, because it often is.

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