

Prophylaxis Strategies for Patients with Acute Venous Thromboembolism

Based on a presentation by Victor F. Tapson, MD

Presentation Summary

Pulmonary embolism is one of the most common causes of unexpected death in hospitalized patients and one of the top diseases leading to medical malpractice lawsuits. In order to effectively prevent venous thromboembolism (VTE), physicians must assess patients' risk factors and stratify their risk accordingly. Studies show general medical patients are most likely to suffer from deep vein thrombosis. Research also indicates that once-daily prophylaxis of such patients with 40 mg of the low-molecular-weight heparin (LMWH) enoxaparin is at least as effective or more effective as prophylaxis with unfractionated heparin, and may be preferable in some populations. It is now being recommended that hospitals develop formal strategies that address the prevention of thromboembolic complications and that general medical patients at risk of VTE receive unfractionated heparin or LMWH.

Within the past decade there has been a dramatic increase in the available knowledge regarding the diagnosis, treatment, and prevention of venous thromboembolism (VTE). Until recently, however, there have been less data about prophylaxis than there are about treatment. New clinical trials are confirming how crucial prophylaxis is in the reduction of the rate of VTE (pulmonary embolism [PE] and deep vein thrombosis [DVT]) among patients at risk of this very serious but sometimes silent medical condition. Accurately assessing patients' risk factors and stratifying their treatment needs accordingly is necessary for successful prophylaxis.

Scope of the Problem

Failure to diagnose and administer prophylaxis for VTE has made it the most common cause of unexpected death in hospitalized patients and 1 of the top diseases leading to medical malpractice lawsuits. Moreover, this rate is likely rising; 25 years ago, approximately 200,000 deaths per year in the United States were attributable to VTE,¹ whereas a more recent study has shown that there are 630,000 clinically significant VTE cases every year in the United States.² The mortality rate from this condition is relatively high, as shown by the data in **Table 1** on the percentage of people admitted to hospitals who die from PE as confirmed by autopsy.³ The percentage of nonautopsy-proven fatal PE cases is doubtless significantly higher.

In the absence of prophylaxis, there is a moderate risk of DVT in this insufficiently studied population of medical patients, as shown in **Table 2**.⁴⁻⁹ The wide variation in the reported rates is largely a result of the different clinical scenarios and protocols under which the studies were conducted. For example, some of the spinal cord injury studies were small, whereas some of the other studies were quite large. Also, the figures for VTE rates following myocardial infarction (MI) are based on studies conducted in the 1970s; with modern management practices including extensive use of thrombolytics, unfractionated heparin, low-molecular-weight heparin (LMWH), and antiplatelet agents, the incidence may be lower today. Notwithstanding these factors, however, substantial numbers of patients still develop

DVT when they do not receive prophylaxis; a study reported that up to 5% of hospitalized medical patients with multiple morbidities and severe immobility may suffer fatal PE.¹⁰

Why Prophylaxis Is Underused

Although the burden of proof clearly rests with the importance of prophylaxis—and current consensus statements recommend prophylaxis—recent surveys show that prophylaxis is still underused in medical settings. There are several reasons for the persistently low rate of VTE prophylaxis. The primary reason is that despite the epidemiologic data demonstrating the prevalence of VTE, clinicians are unaware of the level of thromboembolic risk in medical settings. Second, the patient population is very heterogeneous. This makes risk assessment relatively difficult for most physicians. Third, the significant risk of bleeding prevents many surgeons from administering prophylaxis.

There have also been no large clinical trials on prophylaxis in some patient populations. In other populations in which large clinical trials have been conducted, the diagnostic techniques and the outcome definitions have varied significantly from study to study. This makes it difficult to make cross-trial comparisons and hence draw clinically relevant conclusions.

Risk Stratification

The original triad of risk stratification for DVT was recognized by Virchow in 1856. This consists of the patient’s degree of stasis, the extent of the blood’s hypercoagulability, and the extent of endothelial injury. Today, in order to determine the appropriate level of prophylaxis for each patient, a physician still must accurately assess the level of risk and determine the course of treatment.

One of the most important factors the physician has to take into account is the clinical condition of the patient. This varies according to the type and duration of surgery, the type of anesthesia used, the extent of multiple trauma, and treatment setting (intensive care, inpatient,

Table 1. Autopsy-Proven Fatal Pulmonary Embolism: Percentage of Admissions

General surgery	0.27
Orthopedic surgery	0.42
Infectious diseases	0.43
General medical	0.58
Cancer	1.13

Source: Reference 3.

outpatient, etc.). Today both inpatients and outpatients, including those in nursing homes and long-term care facilities, suffer from increased morbidity than in previous decades and thus are at a higher risk for VTE.

The physician must be sure to take several factors into account when stratifying a patient’s risk for VTE. These include age, previous VTE, advanced malignancy, obesity, prolonged bed rest, severe medical illness, varicose veins, oral contraceptives, MI, and stroke. Age is a significant independent risk factor, particularly in those who are more than 70 years of age. However, even patients older than 50 years appear to be at an increased risk of VTE. The Worcester DVT study examined patients according to age group.² The results showed that although patients aged 40 to 49 years were not at increased

Table 2. The Burden of VTE in Medical Patients: Frequency of DVT in the Absence of Prophylaxis (%)

General medical patients	10-26
Stroke	11-75
Myocardial infarction	17-34
Spinal cord injury	6-100
Congestive heart failure	20-40
Medical intensive care	25-42

VTE = venous thromboembolism; DVT = deep vein thrombosis.

Sources: References 4-9.

risk of DVT, the risk doubled among those aged 50 to 59, quintupled in the 60 to 69 age range, increased 10-fold among those aged 70 to 79, and was 15-fold higher in those 80 to 89.

Women who are pregnant are also at increased risk of VTE. The probability of developing PE and dying is 6 times higher in pregnant women than in women who are not pregnant. In fact, PE is the most common cause of death in pregnant women.

Furthermore, those who travel appear to be at increased risk of developing PE. A recently published article detailed a French trial in which researchers examined the millions of people who pass through Charles de Gaulle Airport each week.¹¹ The researchers found that a significant number of these travelers showed symptoms of PE such as dyspnea up to an hour after they disembarked from planes. It is likely that longer travel results in higher numbers of people with PE; thus, perhaps some people taking transcontinental flights, especially those with additional risk factors, should be considered for prophylaxis before departure.

Having either hereditary or acquired thrombotic disorders also puts patients at increased risk of VTE (Table 3). Unfortunately, although these patients can benefit from prophylaxis, they have not been studied adequately because both

treatment and prophylaxis studies have tended to exclude them. Also, many physicians are likely unaware that their DVT patients may have 1 of these disorders. Just 10 years ago physicians were unaware of factor V Leiden and the prothrombin gene defect, and there may be other thrombotic risk factors to be discovered.

A number of other patient groups are known to have an increased risk of VTE. These include stroke patients, critical care patients, patients with spinal cord injury or shock, those with an uncomplicated MI, those confined to bed (with no other complications) but are more than 60 years of age, or those with a malignant disease. Inflammatory conditions such as systemic lupus erythematosus¹² and inflammatory bowel disease¹³ also increase patients' risk of VTE. Patients with severe cardiopulmonary disease also have been identified as being at moderate risk for VTE, including those with congestive heart failure, pulmonary infection, and respiratory failure.^{10,14,15}

Does Prophylaxis Decrease Mortality?

Three large studies have attempted to assess the impact of thromboprophylaxis on mortality in general medical patients. Unfortunately there are methodologic limitations in each of the studies that cast doubt upon their findings. In 1 study, Halkin et al¹⁶ treated medical patients with either open-label 5000 international units (IU) unfractionated heparin twice daily or no DVT prophylaxis until discharge or mobilization. From the beginning of the trial, mortality was significantly reduced in those receiving unfractionated heparin. However, this effect appeared too early to be explained by a reduction in fatal PE, suggesting that the mortality rate among those receiving unfractionated heparin may have declined through multiple mechanisms.

In a 1996 study by Bergmann and Caulin,¹⁷ acute medical patients were randomized to 7500 IU nadroparin once daily or placebo for 3 weeks. Mortality was similar in both groups. However, the nadroparin group exhibited nonsignificant reductions in the rate of PE found at

Table 3. VTE Risk Stratification: Patient Factors (Molecular)

Inherited	Acquired
Antithrombin III deficiency	Myeloproliferative disease
Protein C deficiency	Hyperhomocysteinemia
Protein S deficiency	Antiphospholipid antibodies
	—Lupus anticoagulant
	—Anticardiolipin antibodies
Heparin cofactor 2 deficiency	
Activated protein C resistance	
Prothrombin G20210A mutation	
Hyperhomocysteinemia	
Elevated factor XI levels	
Elevated factor VIII levels	

autopsy compared with those on placebo (15.9% versus 28.3%, $P = .13$). There were also reductions in clinical VTE (2.9% versus 3.9%, $P = .18$).

In the third study, Gardlund¹⁸ randomized infectious disease patients 55 years and older to 5000 IU unfractionated heparin twice daily or placebo for 3 weeks. Autopsy data were available in 60% of patients who died. Deaths from PE were significantly delayed in the unfractionated heparin group, although the 6-week mortality rate was similar in both groups. Additionally, nonfatal VTE was reduced by unfractionated heparin.

The clinical implications of these studies are unclear because the composition of the patient populations, the methods to detect thromboembolism, and the dosing regimens varied significantly in each one. Comparative studies with clearly defined populations and reliable end points are the only vehicle for confirming that DVT prophylaxis will decrease mortality in at-risk patient populations. Well-designed studies should point to the optimal dose for those in need of antithrombotic therapy.

MEDENOX Study

The Prophylaxis of VTE in Medical Patients with Enoxaparin (MEDENOX) study was conducted using the LMWH enoxaparin in patients immobilized with severe cardiopulmonary disease. It was designed to answer key questions about the need for prophylaxis in this group of medical patients and to determine the optimal dose of LMWH.¹⁵

MEDENOX was a phase III, multicenter, randomized, double-blind, placebo-controlled trial involving 3 parallel arms: enoxaparin 20 mg once daily, enoxaparin 40 mg once daily, and placebo administered subcutaneously for 6 to 14 days. The dose of 20 mg has been shown to be beneficial in certain low-risk surgical patients,¹⁹ but solid safety and efficacy data in medical populations were not previously available. A standard heparin arm was not included, as this drug is much less commonly used in Canada and Europe. Randomized patients had a projected hospital stay of at least 6 days. Routine bilat-

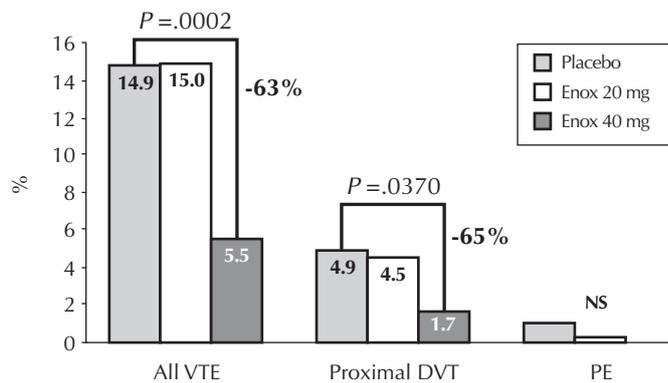
eral ascending venography, which is not readily available in the United States, was performed at days 14 and 90. This is a reliable and accurate method of assessing efficacy of prophylaxis, whereas alternative methods such as clinical diagnosis, fibrinogen uptake test, and duplex scanning are significantly less accurate.

The primary efficacy end point was DVT or PE between days 1 and 14. The secondary efficacy end point was DVT or PE between days 1 and 110. The principal analysis was performed on all patients randomized and assessed for VTE. The safety end points were overall mortality between days 1 and 110, minor and major hemorrhage between days 1 and 14, and thrombocytopenia.

A total of 1109 patients were enrolled from 60 centers in 9 countries, including the United Kingdom, Canada, France, Sweden, Hungary, Switzerland, and Israel. The mean age of the patients was 73.4 years and 50% were male. The median number of risk factors per patient was 2, with some patients having as many as 7 risk factors for VTE. The median treatment duration was 7 days, with 83% of patients receiving treatment between 6 and 14 days.

The inclusion criteria for this study ensured that the patients comprised a clearly defined group within the general medical population. Patients were included if they were older than 40 years; recently immobilized (with an autonomous walking distance of <10 meters) for less than 3 days; had been hospitalized because of heart failure (New York Heart Association [NYHA] class III or IV) or acute respiratory failure (not requiring mechanical ventilation), eg, chronic obstructive pulmonary disease (COPD); or had been hospitalized because of an acute infectious disease, acute rheumatic disorder, or active episode of inflammatory bowel disease and also had a predefined risk factor for VTE. Patients with congestive heart failure and/or pulmonary infections have been highlighted in the most recent American College of Chest Physicians (ACCP) Consensus Statement as requiring DVT prophylaxis.¹⁰

Figure 1. Venous Thromboembolic Events at Day 14 (Principal Analysis)

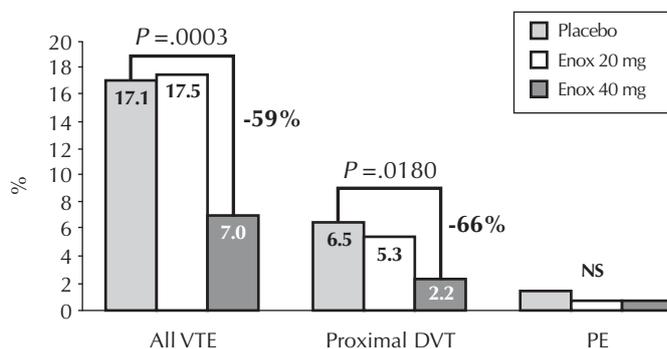


DVT = deep vein thrombosis; Enox = enoxaparin; NS = not significant; PE = pulmonary embolism; VTE = venous thromboembolism.

Source: Reference 15.

Patients with acute infectious disease without septic shock, acute rheumatic disorders, or an active episode of inflammatory bowel disease were only considered eligible if their acute illness was accompanied by at least 1 additional predefined risk factor for VTE. Those included age older than 75 years, previous or evolving cancer, previous history of VTE, obesity (body mass index $>30 \text{ kg/m}^2$ in males and $>28.6 \text{ kg/m}^2$ in females), varicose veins, estrogen/antiandrogen therapy (except

Figure 2. Venous Thromboembolic Events at Day 110



DVT = deep vein thrombosis; Enox = enoxaparin; NS = not significant; PE = pulmonary embolism; VTE = venous thromboembolism.

Source: Reference 15.

replacement therapy for menopause), chronic heart failure, and chronic respiratory failure. The risk factors chosen closely mirror the clinical risk factors defined by the Second Thromboembolic Risk Factors (THRIFT II) consensus document²⁰ and would be expected to increase the likelihood of a venous thromboembolic event. The ACCP guidelines, an international consensus statement,¹⁰ also cite these as risk factors and emphasize their importance when assessing prophylaxis requirements for medical patients.

The exclusion criteria were fairly typical for a prophylaxis study and included pregnancy or possible pregnancy, breast-feeding, stroke or major surgery in the previous 3 months, not being expected to live for more than 3 months, not being able to be observed for the next 3 months, contraindications to iodinated contrast media, thrombophilia, serum creatinine $>150 \text{ mmol/L}$, intubation, human immunodeficiency virus infection, uncontrolled hypertension and conditions conferring risk of hemorrhage, abnormal clotting tests, or hypersensitivity to heparin.

The results of the study show a significant reduction in thrombosis at day 14 among patients receiving prophylaxis with 40 mg enoxaparin (Figure 1). Although the patients who received placebo or prophylaxis with 20 mg enoxaparin had a VTE rate of 15%, patients receiving 40 mg enoxaparin had a rate of only 5.5% ($P = .0002$). The difference was also significant in the more dangerous proximal DVT, with placebo patients and those given 20 mg enoxaparin having a proximal DVT rate of 4.9% and 4.5%, respectively, and those receiving 40 mg enoxaparin having a rate of only 1.7% ($P = .037$). The researchers encountered very few PEs in this screening study. However, patients were not screened for PE and some cases of silent PE may have occurred. As a result, the mortality data were, as expected, somewhat inconclusive. There was also a significant reduction in risk for VTE events at 110 days in patients taking 40 mg enoxaparin (Figure 2).

In addition, the researchers found there was virtually the same low rate of major hemorrhage in all 3 treatment groups (1%

in placebo, 1.5% in enoxaparin 20 mg, and 1.5% in enoxaparin 40 mg), confirming there is no significant risk of major hemorrhage associated with enoxaparin prophylaxis.

There were no significant differences in survival estimates at 3 months among the 3 treatment groups (Figure 3). It is unknown whether there may have been significant survival differences if the patients were observed for a longer period of time or if there had been more patients in the study.

Overall, however, the MEDENOX study results clearly indicate that 40 mg enoxaparin is a more effective prophylaxis regimen for general medical patients—in this case, those patients with heart failure or COPD, who are among the most common nonsurgical patients in the hospital—than 20 mg enoxaparin or placebo.

PRIME Study

The Prevention of Thromboembolism in Medical Patients with Enoxaparin (PRIME) trial examined 959 high-risk hospitalized patients who were randomized to either 40 mg enoxaparin or 5000 IU unfractionated heparin every 8 hours.²¹ The most commonly used regimen of unfractionated heparin is 5000 IU twice daily. Ultrasound scanning was used to diagnose DVT.

The results showed that patients receiving prophylaxis with 40 mg enoxaparin had a DVT rate of 0.2% whereas those on unfractionated heparin had a 1.4% DVT rate. These very low rates may be explained by the fact that ultrasound misses a significant number of cases of asymptomatic DVT.

PRINCE Study

The Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin (PRINCE) study examined 451 German medical patients with severe respiratory disease and heart failure.²² Inclusion criteria closely matched those of the MEDENOX study, with patients in the PRINCE study confined to bed for at least two thirds of their waking hours and therefore at risk of DVT. Patients were randomly assigned to either 40 mg enoxaparin once daily or 5000 IU unfractionated heparin

every 8 hours. The study population was subdivided into 2 groups: 245 patients with severe respiratory disease were examined in PRINCE I and 206 with NYHA class III or IV chronic heart failure were examined in PRINCE II.

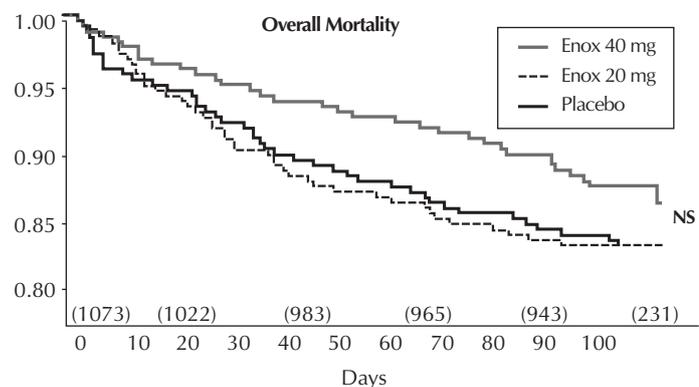
PRINCE patients receiving prophylaxis with enoxaparin had a lower incidence of DVT than those given unfractionated heparin: 5.9% versus 7.1% in PRINCE I ($P = .19$) and 9.7% versus 16.1% in PRINCE II ($P = .01$). There were insignificant rates of major hemorrhage in all of the patient populations and there was no thrombocytopenia seen in those taking enoxaparin.

The researchers concluded that 40 mg enoxaparin is at least as effective as 5000 IU unfractionated heparin every 8 hours for prevention of DVT and PE in patients with cardiopulmonary disease. They also determined that there is a higher incidence of VTE in patients with congestive heart failure than in those with severe respiratory disease.

Why Enoxaparin?

Enoxaparin is the LMWH for which the most preliminary data have been gathered, and the US Food and Drug Administration has approved it for a number of DVT pro-

Figure 3. Survival Estimates at 3 Months



Kaplan-Meier estimate: log-rank test, enoxaparin 40 mg versus placebo: $P = .30$; hazard ratio: 0.90; 95% Confidence Interval [0.7 to 1.1].

Enox = enoxaparin; NS = not significant.

Source: Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group (MEDENOX). *N Engl J Med* 1999;341:793-800. Reprinted with permission.

phylaxis indications. Based on the results of the MEDENOX study, enoxaparin is approved for prophylaxis of DVT with or without PE and acute coronary syndromes. This drug is also approved for DVT prophylaxis in patients undergoing total hip and knee replacements, as well as for prophylaxis in general surgery and medical patients. Enoxaparin is the only drug approved for prophylaxis of general medical patients.

VTE Prophylaxis May Fail

The efficacy of a physician's prophylaxis may be as important to a patient's outcome as the decision to administer prophylaxis. A study published in the past year indicated that patients who had VTE were more likely to have these events if they were on prophylaxis than if they were not receiving prophylaxis.²³

In this study, Goldhaber et al²³ reviewed charts from the hospital for DVT and PE patients, and examined which patients were receiving prophylaxis and the methods of prophylaxis. Sixty percent of the 384 identified patients had undergone surgery within the previous month. Of the 384 patients, 272 had DVT alone, 62 had PE alone, and 50 had both.

The researchers had expected to find that most DVT events occurred among those who had not been receiving prophylaxis. What they found, however, was that most events took place in patients receiving prophylaxis. Furthermore, the team found that most of those who suffered venous thromboemboli were medical service patients; fewer than 25% were general or orthopedic surgery patients. Goldhaber et al²³ also found that 33.8% of patients who developed VTE were receiving prophylaxis with unfractionated heparin alone, 28.8% were receiving prophylaxis with a mechanical/pharmacologic combination, and only 1.5% had been given LMWH (Table 4).

Rather than concluding that prophylaxis is not useful, it is thus important to consider that the prophylaxis regimens that might result in fewer events, such as LMWH, should be considered more often. They also noted that risk stratification must be done very carefully and accurately.

Recommendations

On the basis of all of these studies, the ACCP developed general recommendations for prophylaxis in its most recent 6th Consensus Conference on Antithrombotic Therapy.¹⁰ It was recommended that every hospital develop a formal strategy that addresses the prevention of thromboembolic complications. The organization recommended that this be in the form of a written thromboprophylaxis policy. The ACCP also recommended that physicians use low-dose unfractionated heparin or LMWH in general medical patients with risk factors for VTE including cancer, bed rest, heart failure, and severe lung disease.

As data accumulate, it is quite possible that the next set of recommendations will include an increased emphasis on LMWH in both general medical inpatients and outpatients. This will reflect the fact that many very sick medical patients who are released from the hospital are still at high risk for DVT.

Conclusion

The importance of correct prophylaxis to minimize mortality and morbidity should not be underestimated. Proper risk

Table 4. Prophylaxis Modalities in Patients Who Nevertheless Developed Venous Thromboembolism

Modalities	Number of Patients (%)
Unfractionated heparin only	68 (33.8)
Mechanical/pharmacologic combination	58 (28.8)
Warfarin	32 (15.9)
Compression boots	20 (10)
Anticoagulation combination	9 (4.5)
Vascular compression stockings	9 (4.5)
Low-molecular-weight heparin	3 (1.5)
Stockings + compression boots	2 (1)

Source: Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest* 2000;118:1680-1684. Adapted with permission.

stratification and an effective pharmacologic prophylaxis regimen are necessary because there are so many patients in many medical settings who require prophylaxis, including general medical and surgery patients, those in the intensive care unit, and outpatients in nursing homes and other long-term care settings.

As the late Paul Eggermayer wrote, “The energies of physicians treating patients with DVT would be more profitably channeled into improving the current dismal rates of prophylaxis, since there can only be a limited advantage to encouraging increased alertness for a disease that is usually asymptomatic.”²⁴ Eggermayer pointed out that “the real problem is not the 10% of patients who survive long enough to receive treatment but the 90% who die in the first hour after the event. For both groups, more systematic prophylaxis is clearly the way forward.”

... DISCUSSION HIGHLIGHTS ...

Legal Issues

Dr. Perler: There is a senior surgeon at our hospital who has very publicly stated, somewhat tongue-in-cheek but not totally, that if the patient has a PE that’s God’s complication, and if they bleed into their belly that’s his complication. I think a lot of surgeons practice under those guidelines and don’t really use prophylaxis unless it’s a very obviously high-risk patient, and this approach clearly continues to be an enormous problem. About once a year I get a case sent by a lawyer for heparin-induced thrombocytopenia, but I don’t think I’ve ever received a case of someone being sued for lack of prophylaxis. How big an issue is that? Do you have any kind of real data?

Dr. Michota: It’s coming. There are junior attorneys out there who know as much about thrombosis as anybody in this room. Along with the ads in the papers that say, “Have you been involved in an accident?” we’re now going to see ads that say, “Have you lost a loved one in the hospital recently?” And the first thing they’re going to look at is whether the patient was receiving prophylaxis as recommended by consensus

bodies. They just haven’t had an opportunity to get to the courts yet, but they will.

Dr. Tapson: I get calls every few weeks from attorneys’ offices asking if I want to be involved in a PE case. They’re usually failure to diagnose or lack of prophylaxis cases. So I can just tell you from the phone calls that they’re already there, and I think that we’re just getting the tip of the iceberg so far.

Sequential Compression Devices

Dr. Perler: Obviously there are mechanical means for preventing DVT, and in certain patient populations, sequential compression devices have shown well-documented efficacy. In the real world, however, these devices are often not properly used the way they are in clinical trials. There are numerous observations of patients who had the devices applied, but they weren’t plugged in. There are patients who had the devices applied and plugged in, but it wasn’t turned on. There are patients whose devices were applied, but they were hanging off the legs. A study documented these problems in a significant number of cases. Although you can avoid the risk of hematoma, bleeding, and those kinds of surgical complications, I think sequential compression devices, in practical terms, may be inferior to pharmacologic prophylaxis on a day-to-day basis.

Dr. Michota: It is true that sequential compression devices are only effective if worn continuously. However, even when they are applied properly, there are major disadvantages to their routine use. Studies have demonstrated that these devices destroy sleep hygiene, and can actually induce delirium in hospitalized elders. Furthermore, sequential compression devices tie patients to the bed, which limits the best form of prophylaxis, which is ambulation. The first thing we try to do is get our patients out of bed as soon as they can, and if you have them hooked to a compressor, it makes it very difficult to do that. Perhaps the most ideal patient for sequential compression devices is a bed-bound functional class IV who you’re not expecting to move. Unfortunately, that type

of patient is in the highest risk category, and it has been demonstrated that sequential compression devices are inferior to pharmacologic prophylaxis in this group.

LMWH

Dr. Groce: How can we afford to administer prophylaxis to all of the patients that we know should be given something more expensive than low-dose unfractionated heparin? How can we begin to develop means and templates of screening for the most appropriate patient to achieve outcomes of efficacy and safety and to be given LMWH therapy versus, perhaps, unfractionated heparin?

Dr. Michota: My patient population is primarily inpatient geriatric and almost all of them have more than 3 independent risk factors for thrombosis. I have found the MEDENOX trial to be incredibly convincing and I think if you went through most hospitals in the United States you'd be hard-pressed to find too many inpatients these days who are not at least moderate risk. I would suggest that the majority are actually high risk. Because of that, you really have to wonder whether 5000 IU bid of unfractionated heparin is really appropriate. We know that in the high- and very-high-risk surgical patients, unfractionated heparin just doesn't do the job. We also know from case-series data that secondary DVT in medical patients is more likely the result of failed unfractionated heparin prophylaxis. Because the majority of my patients are at high risk, I don't use a lot of unfractionated heparin for prophylaxis; they are on LMWH.

Dr. Thapar: How long do you anticoagulate the patients that have DVT?

Dr. Tapson: In the short term, we would treat with LMWH for at least 5 days until the international normalized ratio is therapeutic for 2 consecutive days. Longer term, we used to recommend 3 to 6 months. I think people are tending to treat a bit longer now, some of which is probably based on a publication by Kearon et al in *The New England Journal of Medicine*

a few years ago.²⁵ Those were idiopathic and thrombophilic patients. It was quite clear in those patients that 3 months was not long enough, and they stopped the study early because of the recurrence rates in the 3-month group. So I think my tendency is to treat almost everyone for 6 months. You probably saw the publication by Agnelli et al recently in *The New England Journal of Medicine*.²⁶ They found that if you treat 1 group for 3 months and another group for 1 year, the group treated for 1 year does much better in terms of recurrence, but when you stop that treatment at 1 year, that 1-year group reverts and starts to have recurrence rates just like someone being treated for 3 months.

Dr. Michota: This speaks to the fact that many patients have nonmodifiable risk factors that will remain indefinitely. Systemic anticoagulation for a finite period of time ignores the fact that they have ongoing risk factors that never go away. Once you stop anticoagulation, you start seeing recurrent thromboembolic events, just simply because of the patient profile that already exists.

Dr. Hoffman: What about the dose? The 20- and 40-mg doses of enoxaparin seemed to work in the MEDENOX study. I just wondered how the doses were arrived at.

Dr. Tapson: Well, 20 mg was hypothesized as probably not being adequate, based on its usefulness in certain lower-risk, surgical populations but not in very high-risk populations. With the data on total hip replacement first being 30 mg every 12 hours, and then finding 40 mg once per day was successful in a moderate-to-high-risk population of patients made people comfortable with the 40-mg dose. I would still worry that in a patient who weighed 300 or 400 pounds, 40 mg would not be enough. Maybe it is; maybe the drug is so bioavailable that 40 mg does work and we don't need any more than that, but I have had a tendency to use 60 mg in heavier patients as prophylaxis, but it's completely empiric and not based on data.

Diagnosing Recurrent DVT

Dr. Thapar: How do you diagnose recurrent DVT as opposed to a new event?

Dr. Michota: That's a challenge. Obviously, if you have a previous imaging study for comparison, you can differentiate between chronic and acute based on a new DVT location.

Dr. Thapar: It's recommended that when you stop treatment, be it after 3 or 6 months, that you get a baseline. Both an impedance plethysmography (IPG) and an ultrasound should be done because each has some limitations. Suppose you have done an IPG on the last day of treatment, and you realize what the flow was. If the patient comes back with symptoms and if the IPG is substantially different, then you know this is a new event.

Dr. Michota: Duplex ultrasonography can differentiate between acute and chronic thrombus without a baseline study. It does get tricky, though, if the venous system is not well visualized or the events are staggered very close together. In somebody with significant postthrombotic syndrome, nuclear venography, which actually tags activated platelets, can help differentiate acute versus chronic thrombus.

Dr. Perler: I think the most challenging group of patients is the group with already established postphlebotic syndrome, because it is not uncommon for a patient with postphlebotic syndrome to have an exacerbation of swelling, tenderness, and redness, even in the absence of recurrent acute DVT. Those are the patients in whom I still think there is a role for venography, but they're fairly infrequent patients.

Dr. Tapson: We've had the best luck with magnetic resonance imaging (MRI). Right now, we're reviewing the last 5000 MRIs we've done for suspected DVT. In reviewing the first few hundred cases, we found that about 20% of cases were read as a previous or chronic DVT, that is, based on collateral vessels, vessel

narrowing, webs, and other factors. MRI isn't always possible, though, and it's expensive. Our pharmacoeconomics group may have some difficulty if we can't prove that it makes a difference, but the technology is unbelievable. Computed tomography scanning is getting better as well.

Prophylaxis Implementation

Dr. Wales: How do you take these data to your hospital and get the physicians, the administrators, and the system to understand it?

Dr. Tapson: We haven't finished researching prophylaxis. I think the best way to do it is to create a multidisciplinary group with those with expertise, including those in nursing and pharmacy. The group should meet on a regular basis and hone these guidelines. The final recommendation might not be that every patient receives prophylaxis with 40 mg enoxaparin once a day, but I think that should be on the list for the moderate- or high-risk patients. Then you present the data, saying, "Look, this is what our group has decided. This is the right thing based on mortality, postphlebotic syndrome, recurrences, nursing work, cost, everything," and hope that your argument is going to be effective.

Postphlebotic Syndrome

Dr. Perler: PE gets all the attention because, in its most severe manifestation, it represents a threat to the viability of the whole patient. Postphlebotic syndrome is the poor sister because it doesn't threaten the viability of the limb, and it doesn't threaten the viability of the patient—but it is clearly the most common complication of DVT. Numerous studies show the vast majority of patients who have had 1 episode of proximal DVT will develop some of the signs and symptoms of the postphlebotic syndrome during the next 2 to 10 years, and it is a cause of enormous morbidity and physical disability. At least 20% of patients with postphlebotic syndrome never had a proximal DVT documented clinically, and I'm sure some of

those patients had calf vein thrombi. Increasingly, we're seeing patients who only had calf vein thrombi go on to develop venous insufficiency.

Dr. Thapar: It's rather dismal, though, that the postphlebotic syndrome is not as dramatically reduced as one would imagine, because studies have shown that even after you treat patients with either unfractionated heparin or LMWH, almost 30% of them will develop, at 5 years, postphlebotic syndrome, because you do not dissolve the clot entirely.

Dr. Perler: The goal should be prevention, not just to prevent PE but to prevent this long-term chronic disease that results from DVT.

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