Current and emerging treatment options for venous thrombosis: A case discussion

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Case presentation

Moderator: The patient is a 56-year-old obese female brought to the emergency department by her husband. Her chief complaints are chest pain, shortness of breath, and light-headedness. She weighs 200 lb and is 66 inches tall. She says that her symptoms started with left calf pain approximately two days ago, and last night she started feeling short of breath and had chest pain. She could not sleep, and her shortness of breath had become progressively worse over the past several hours. Vital signs, electrocardiogram (ECG), cardiac enzymes, complete blood count, comprehensive metabolic panel, chest x-ray, and a ventilation-perfusion (V/Q) scan of the lungs were ordered in the emergency department. She was admitted for treatment of pulmonary embolism (PE). She is postmenopausal and has type 2 diabetes mellitus and high blood pressure. She currently takes lisinopril, rosiglitazone, aspirin, and conjugated estrogens. She has no known drug allergies, and her sexual history is noncontributory to her current condition. At the time of admission, her blood pressure (146/92) and heart rate (96 beats/min) were slightly elevated. The ECG indicated that she was in normal sinus rhythm. The chest x-ray revealed that her heart was slightly enlarged. The radiology report stated that the results of the V/Q scan were highly probable of pulmonary embolism. Cardiac enzymes were negative. Hematology and blood chemistry results were all normal, with the exception of an elevated serum creatinine (SCr) (2.3 mg/dL).

Acute treatment considerations

Question: Is there any missing information that you would consider critical for making appropriate decisions about this patient’s treatment?

Dr. Haines: First, it is critical to confirm the diagnosis before we can consider treatment with antithrombotic drugs. The patient’s presentation is classic for PE, including her shortness of breath and chest pain preceded by leg pain.1 It is uncommon for patients to have the entire constellation of symptoms, and, even when they do, objective testing is always required to confirm the diagnosis.2 The V/Q scan is a reasonably specific but not very sensitive test. It is used less frequently in clinical practice today, as many institutions prefer using spiral computed tomography scans. Given her symptoms and the results of the V/Q scan, there is little question about the diagnosis. Unfortunately, we do not often get such definitive results from V/Q scans, and additional tests are sometimes needed.

The next question is, Is additional information needed to make appropriate short- and long-term decisions about treatment? I would try to explain the etiology of the event. Why did this 56-year-old woman get a PE? To determine the likely etiology, I would look for risk factors for venous thromboembolism (VTE) (appendix). The identification of these risk factors is important for preventing VTE during hospitalization and for making treatment decisions for patients who develop a deep venous thrombosis (DVT) or PE.3 Determining the etiology of the event will help us determine the length of antithrombotic therapy. One factor that places a person at very high risk
for VTE is a previous DVT or PE; recurrent events should be treated indefinitely. There is no history of DVT or PE in this patient, but I would carefully question her about it. As she is 56 years old, her age is not a particularly strong risk factor. The risk of VTE doubles with each decade over 40 years of age. When patients are in their 80s or 90s, VTE becomes a very substantial risk. I would want to know if this patient recently had surgery, and, if so, was it major or minor surgery. The case presentation does not specify whether the patient has been recently hospitalized with a major medical illness or trauma. Perhaps she has been immobile for a prolonged period of time. If so, we could probably attribute the DVT or PE to one of those events and would therefore recommend antithrombotic therapy for a relatively short period of time.

Does she have cancer? Again, it is not stated in the case presentation, but if she has a history of cancer I would make very different decisions about what drugs I would initially recommend and how long she should use them. So far, she has relatively few risk factors for VTE other than her age. My immediate impression is a possible underlying hypercoagulable state. Three or four times as many women are prescribed estrogen replacement therapy, which, in my judgment, is the most likely etiology of this event or at least a contributing factor. Any of the selective estrogen-receptor modulators, such as raloxifene and tamoxifen, are also potential culprits.

In addition to etiology, the severity of the event must be considered, as it dictates whether the patient is admitted to the hospital or to an intensive care unit. To determine the severity of the PE, I would need to know if oxygenation is being compromised. Is the patient in visible distress? Arterial blood gases or pulse-oxygen measurements would help us make that determination. She may need to be incubated for ventilation support. This information was not provided, so it is difficult to determine the severity of this episode.

Dr. Nutescu: I agree with Dr. Haines’s comments regarding the evaluation of the patient for known risk factors for VTE. In addition to the factors he mentioned, I would consider a few more at baseline. As this patient is obese, there is a high likelihood that she may not be very physically active. It is important to document her immobility as not only a risk factor for VTE but a determining factor in the length of anticoagulation therapy. Patients with ongoing, chronic risk factors should receive anticoagulation therapy for a longer duration, even with the first VTE. If there is a family history of VTE or hypercoagulability, she has a greater risk for recurrent VTE, and a hypercoagulable workup should be strongly considered. Evaluating the patient’s renal function at baseline may dictate the choice of anticoagulant. This patient had a Scr of 2.3 mg/dL at the time of admission and, depending on the method of calculation, a creatinine clearance (CLcr) of 20–30 mL/min. We need more information about her renal status to determine whether she has chronic kidney disease in light of her diabetes versus an acute change in renal function. Getting a good, detailed history of any nonprescription medication use is also critical, as this may not only determine which anticoagulant is used but also the appropriate initial dose of some anticoagulants, such as warfarin. Finally, the reliability of the patient and the potential for compliance with therapy need to be evaluated and documented. It may be difficult for some patients to administer s.c. LMWH injections at home and adhere to warfarin therapy. The benefits versus the risks of such therapies must be evaluated on the basis of the patient’s ability to comply with the prescribed regimen. All of these factors collectively play a role in the selection of the most appropriate acute and chronic anticoagulant regimen for this patient.

Question: Do you think this patient needs to be hospitalized? Why or why not? On what criteria are you basing your decision?

Dr. Nutescu: The first thing we have to consider is the patient’s clini-
clinical status. How stable is she? She has an acute symptomatic PE and appears to be hemodynamically stable. The current standard of practice in the United States for patients with acute PE is hospital admission, at least for an immediate observation period and an initial course of anticoagulation therapy. Based on this patient’s clinical presentation and the available literature, I would recommend admitting her. If after a few days of therapy she is clinically stable and has no complications or other reasons to stay in the hospital, she may be discharged early, and the transition over to chronic therapy can be completed in the outpatient setting.

Dr. Haines: I concur. The standard of practice is “admission, admission, admission.” I do not think there are many places, at least in the United States, that would treat a patient with a symptomatic PE on an outpatient basis. Even the most progressive institutions with a well-managed outpatient DVT treatment program would admit this patient for at least 24 hours for observation. I think hospital admission is absolutely required in this case.

Question: Do you think this patient should receive thrombolysis? On what criteria are you basing this decision?

Dr. Haines: The use of thrombolytic agents in DVT or PE is controversial. The data are not particularly compelling, and the use of thrombolytic agents is fraught with potential dangers. There is a substantial risk for major bleeding and intracranial hemorrhage. There are some short-term benefits (Table 1) with the use of thrombolytics. Reperfusion in the pulmonary artery at two hours and one day is improved. At one week and one month, the reperfusion rate is essentially the same when compared with placebo. While the pulmonary artery may be opened up a bit quicker it does not really make a clinically important difference for most patients in the long run. However, if the PE is very large, it can be life threatening. If the patient has had syncope or is in circulatory shock, thrombolysis is justified. Many experts recommend using a thrombolytic agent if there is any evidence that the heart is somehow being affected (e.g., evidence of right ventricular dysfunction). Alternatively, the patient can be sent to surgery for a thrombectomy; however, most institutions do not have a surgeon with sufficient experience in performing this procedure.

Dr. Nutescu: I agree with Dr. Haines. In our institution, we would use an injectable anticoagulant for the immediate acute treatment of this patient. Only if her clinical status worsened (e.g., if she becomes hemodynamically unstable) would we consider a thrombolytic. However, based on her current clinical presentation, we would not use a thrombolytic.

Question: What acute treatment regimen would you recommend? Would you use UFH by i.v. infusion or an LMWH? What about fondaparinux? Explain the rationale for your choice.

Dr. Nutescu: The sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recommends either i.v. UFH or s.c. LMWH for the acute treatment of VTE. Both of these treatment options are grade 1A recommendations by ACCP, which is the strongest possible recommendation based on the evidence. In addition, the LMWHs are recommended over i.v. UFH for the treatment of VTE (grade 1B recommendation). This preference for LMWH is based on convenience and ease of drug administration, the ability to discharge patients to home sooner and treat them in the outpatient setting, an efficacy advantage in cancer patients, and a potentially better efficacy and safety profile. However, this efficacy and safety benefit is mainly based on meta-analysis. Individual trials comparing LMWH with i.v. UFH for the treatment of VTE show similar safety and efficacy profiles. If i.v. UFH is selected, the guidelines recommend that a weight-based dosing regimen be used, such as an 80-units/kg bolus dose followed by an 18-units/kg/hr maintenance infusion. A weight-based dosing regimen for i.v. UFH is preferred because therapeutic activated partial thromboplastin times (aPTTs) are attained sooner than with standard or fixed-dosing schemes. If a LMWH is used, we have to select a specific product and follow appropriate dosing guidelines for that particular product (Table 2).

Currently there are three commercially available LMWHs in the United States: dalteparin, enoxaparin, and tinzaparin. Even though all three agents have been used to treat VTE, only enoxaparin and tinzaparin have Food and Drug Administration (FDA)-approved labeling for the treatment of DVT with or without PE. Dalteparin is approved for this indication in some European countries and Canada. In choosing an LMWH, the convenience of administration and dosing also need to be considered, as some of the agents are administered once a day (tinzaparin), whereas others have slightly more favorable data regarding the treatment of PE with twice-daily dosing regimens (enoxaparin). It is

Table 1.

**Benefits of Thrombolysis for Pulmonary Embolism**

<table>
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<tr>
<th>Variable</th>
<th>% Improvement in Pulmonary Artery Perfusion over Time</th>
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<tr>
<td></td>
<td>Two Hours</td>
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<tr>
<td>Thrombolysis</td>
<td>12</td>
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<td>No thrombolysis</td>
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important to note that most of the
efficacy and safety data for the treat-
ment of PE with dalteparin and
enoxaparin are from DVT studies in
which approximately one third of the
patients had a concurrent PE. The
only clinical trial to date that specifi-
cally evaluated the efficacy of an
LMWH in patients with acute symp-
tomatic PE compared s.c. tinzaparin
once daily with i.v. UFH and found
tinzaparin to be as safe and effective
as UFH.12

My personal preference for this
patient is to initiate treatment with
an LMWH. LMWHs have a better
safety profile than UFH, including a
lower rate of HIT. They have a much
more predictable anticoagulant effect
than UFH and do not require routine
anticoagulation monitoring or dos-
age adjustments, unlike UFH. Fur-
thermore, LMWHs allow for an
easier transition to the outpatient
setting, provided that the patient is
otherwise clinically stable. We are fa-
miliar with the disadvantages and the
difficulty in dosing and monitoring
UFH. We know that the response to
UFH is very unpredictable due to a
myriad of contributing factors, such
as nonlinear kinetics, wide interindi-
vidual variations, heparin resistance,
and problems with aPTT test reliabil-
ity. Proper dosing of UFH is a com-
plex clinical issue, and often it is very
difficult to attain a therapeutic aPTT
within the first 24 hours of initiating
therapy. Often clinicians follow com-
plex dosing schemes that are labor-
intensive and tedious. Despite our
best efforts, the rates of attaining and
maintaining therapeutic aPTTs are
less than optimal. Not attaining a
therapeutic aPTT within the first 24
hours of initiating therapy in patients
with acute VTE has been linked to
both poor short- and long-term out-
comes. Data suggest that failure to
achieve a therapeutic aPTT in the
first 24 hours after initiating UFH
therapy results in a fourfold higher
incidence of recurrent events com-
pared with patients in whom a ther-
apeutic aPTT is achieved.13 One argu-
ment that is often raised by clinicians
is that in their practice they do an
excellent job with dosing UFH using
nomograms. The problem with this
approach is that, although heparin-
dosing nomograms may increase the
likelihood of attaining therapeutic
aPTTs, audit data show that approxi-
mately 25% of patients do not
achieve adequate anticoagulation
within the first 24–48 hours, despite
the use of these protocols.14 There-
fore, I would favor using an LMWH
versus a UFH for the initial treat-
ment course. Now the next logical
question to ask is, which LMWH
should we select? Based on the avail-
able data, my personal preference is
to use tinzaparin to treat acute symp-
tomatic PE.15 Other reasons for
choosing tinzaparin over the other
two LMWHs in this particular pa-
tient relate to her weight and renal
function. In obese patients, enox-
aparin given once daily appears to be
slightly less effective than tinzaparin,
although this may be due to the lower
daily dose used with this regi-
men.16 The dosing of dalteparin is
weight-based, but a maximum dose
of 18,000 units per 24 hours was used
in most VTE studies.17 This can be
problematic in obese patients, as
anyone who weighs more than 83 kg
receives a fixed dose of dalteparin. It
is unknown whether these lower dos-
eses would have a negative impact on
efficacy in obese patients. In contrast,
tinzaparin can be administered once
daily in obese patients and has no
maximum dosage limit. Renal im-
pairment is another factor to consid-
er with this patient. In patients with a
CLc of <30 mL/min, LMWHs accu-
mulate at different rates. Tinzaparin
has a 20% accumulation rate versus
enoxaparin’s 40–50% accumulation
rate.18 Among the three LMWHs,
dalteparin has the most limited data
in this patient population. Therefore,
for short-term use, such as in this patient, tinzaparin may not require an initial dose reduction, whereas enoxaparin doses will have to be adjusted and anti-Xa levels monitored. [Authors’ note: As of April 2004, specific dosing guidelines became available for enoxaparin in patients with renal impairment.19] In patients with a CLcr of <30 mL/min, a once-daily administration of enoxaparin 30 mg s.c. is recommended if the agent is used for prophylaxis of VTE, and once-daily administration of enoxaparin 1 mg/kg s.c. is recommended if the agent is used for the treatment of VTE or acute coronary syndrome. No dosage adjustment is recommended for patients with a CLcr of 30–50 mL/min. If this information had been available at the time of this presentation, the treatment and dosing decisions would most likely differ.

Fondaparinux would also be a very good choice for the initial treatment of VTE in patients with normal renal function.20,21 Fondaparinux has a half-life of approximately 17 hours and is eliminated through the kidneys. Therefore, it would not be my preferred choice in this patient in light of her renal status. The recently published Matisse PE study compared once-daily s.c. fondaparinux with i.v. UFH in the treatment of acute symptomatic PE.21 In this large study of over 2000 patients, fondaparinux was found to be as safe and effective as UFH. This agent now offers another alternative for the treatment of PE.

**Dr. Haines:** I completely agree. Fondaparinux would not be an option in this case until we get data about how to use it in patients with significant renal impairment. Among the LMWHs, tinzaparin is not readily available in most hospitals, and it is not on our formulary. Therefore, I would use UFH by i.v. infusion, primarily because this patient has significant renal impairment. While not perfect, we do have a reasonably good system to check aPTTs daily to monitor a patient’s anticoagulation response. I would treat her with i.v. UFH for at least 48 hours and then consider using an LMWH if she is medically stable. Dr. Nutescu reviewed some data that indicate that if the aPTT is not above the therapeutic threshold within the first 24 hours, the short- and long-term outcomes are adversely affected. However, it is important to keep in mind that most of these data are from retrospective analyses. We know from prospective clinical trials that i.v. UFH performs as well as LMWHs and fondaparinux. There are no data to suggest that these drugs are superior to i.v. UFH in a setting where therapy is well managed. As long as there is someone available who has experience managing UFH who will check the aPTT frequently and adjust the dose appropriately, I think i.v. UFH is the preferred treatment in this circumstance. If I worked in a setting where a good monitoring system were not in place, then I would probably recommend tinzaparin or enoxaparin.

**Dr. Nutescu:** I agree that UFH would be easier to monitor via aPTT testing in light of this patient’s renal function; however, despite close monitoring and frequent dosage adjustments, i.v. UFH is not a safer option, and bleeding still occurs in renally impaired patients. In a recent study, similar bleeding rates were reported with adjusted-dose monitored i.v. UFH and fixed-dose LMWH in patients with renal impairment (CLcr < 30 mL/min).22 An additional consideration when selecting a specific LMWH is the price of the product. Tinzaparin is commercially available in the United States and has the lowest wholesale price of the three LMWHs. This may be important when patients must continue therapy in the outpatient setting and pay out of pocket. Formulary restrictions may limit your choice of the agent in the inpatient setting.

**Dr. Haines:** Be careful—the average wholesale price may not be representative of your costs. Hospital contracts for enoxaparin or dalteparin may be very competitively priced for inpatient use. I agree that enoxaparin is often more expensive in the outpatient setting, which is a critical factor when your patient is paying out of pocket. We occasionally use tinzaparin in my practice because the volume of the injection is smaller. For a morbidly obese patient, the 20,000-units/mL concentration can be used to administer relatively large doses in a single small-volume injection, unlike some of the other LMWHs.

**Question:** Could you comment on the labeling of enoxaparin? One of the leading discussions we have at our hospital is that the FDA labeling specifically states that enoxaparin is indicated for DVT with or without PE. You are discussing its use in acute PE, which is not a labeled indication.

**Dr. Nutescu:** With the exception of the tinzaparin trial previously mentioned, there have been no large acute symptomatic PE studies with LMWHs. Most of the PE data come from DVT trials, and the FDA labeling for both enoxaparin and tinzaparin states that they are indicated for the treatment of DVT with or without PE. However, given that PE is included in the labeling, I do not see any legal risk involved with the use of an LMWH in this case. It is interesting to note that, given the recently published Matisse PE study, fondaparinux will most likely be indicated for the acute treatment of PE.21

**Dr. Haines:** Because this patient’s leg pain preceded the PE, I feel comfortable concluding that she indeed had a DVT; therefore, I do not believe we are using these products for off-label indications.

**Question:** Given this patient’s renal dysfunction and obesity, would you check anti-factor Xa serum ac-
tivity? What role does it really play in managing patients?

**Dr. Nutescu:** The monitoring of anti-Xa serum activity in patients who receive LMWHs is very controversial, as there are no conclusive data connecting it with efficacy or safety outcomes. However, guidelines based mainly on expert opinion state that measuring anti-Xa serum activity can be beneficial in certain circumstances, such as obesity, renal impairment, pediatric patients, and pregnant patients. Anti-factor Xa activity levels serve as a biological marker for determining how much drug is in the patient’s system and may help to make reasonable dosing decisions. Given this patient’s weight (91 kg), monitoring of anti-Xa activity is not recommended. In the vast majority of cases, LMWH can be dosed using actual body weight. The heaviest patients studied to date weighed 160 kg. Patients who weigh more than 160 kg should still be dosed using actual body weight, but measurement of their anti-Xa activity may be justified. In patients with renal impairment, measurement of anti-Xa activity may be justified to determine if there is accumulation of the drug. This is especially important in patients with a CLcr of <30 mL/min and if a LMWH has been used previously for more than a few days.

### Chronic treatment considerations

**Question:** Assuming that you will also prescribe warfarin for long-term anticoagulation therapy for this patient, when would you start warfarin therapy, and what dosage would you give her?

**Dr. Haines:** Warfarin is clearly indicated and should be started on day 1. If you are using i.v. UFH alone, whether or not you should wait until the aPTT is therapeutic is controversial. I give warfarin the very first night, regardless of the aPTT, provided that i.v. UFH was actually started. Some institutions have a policy against initiating warfarin therapy until a therapeutic aPTT is documented. Once you initiate warfarin therapy, it should be adjusted based on the International Normalized Ratio (INR). Some clinicians are overly zealous about making warfarin dosage adjustments, making them too frequently or too aggressively. Although we usually measure the INR daily, I generally wait two or three days to see what the INR is before I make any adjustment. Many clinicians react when there is no change in the INR after the first dose and automatically increase the dosage. That is a mistake. These clinicians end up inappropriately increasing and decreasing the dose every day because they are reacting to changes in the INR (or lack thereof). You must allow some time for the effect to occur. You can stop the i.v. UFH or LMWH once a therapeutic INR is attained.

There is considerable controversy regarding the initial dose of warfarin. In recent years, we have been using lower and lower doses when initiating warfarin therapy. Several years ago it was common practice to give everyone 10 mg for two days. Recent studies suggest that many patients become overanticoagulated when 10 mg is used. Based on these data, the current recommendation has been to start everyone with a 5-mg dose. I believe both of these “one dosage fits all” approaches are inappropriate. The initial dose should be based on individual patient factors, such as age, medical status, liver function, serum albumin concentration, concurrent drug use, and previous response to warfarin therapy. Also, patients who are managed as inpatients for an acute thrombotic event can and should be treated a bit more aggressively. Many, perhaps most, patients should start with 5 mg of warfarin, but there are some patients who should receive 2.5 mg initially and others should start with 7.5 or even 10 mg. In this particular case, I would recommend starting with 10 mg. This patient is relatively young, she is being monitored closely in a hospital, and I have no reason to believe that she would be unusually sensitive to warfarin. Furthermore, this was an acute event. We are not using warfarin for primary stroke prophylaxis in a patient with atrial fibrillation, where there is no urgency to get the INR to a therapeutic level. In this case, we want to get a therapeutic INR as quickly as possible. If we take too conservative an approach, it has cost implications in terms of length of hospital stay and length of i.v. UFH or LMWH therapy. I would never recommend an initial dose that exceeds 10 mg unless I knew the patient required more than 10 mg in the past. Given her age, I would anticipate that her maintenance dosage will probably be somewhere between 5 and 10 mg a day, but would not be surprised if it were substantially lower or higher than what the “average” person requires. Frankly, there is an art to warfarin dosing, and no one has devised a formula that can accurately estimate the best initial dose for a given patient.

**Dr. Nutescu:** I agree. The 2001 ACCP guidelines still recommend initiating warfarin at 5 mg daily. However, since the guidelines were published, additional data became available supporting higher warfarin doses at initiation, such as 10 mg. Personally, I avoid the “fixed dose fits all” approach and individualize initial warfarin doses using specific patient characteristics, such as indication, age, weight, race, concurrent medications, dietary habits, and concurrent disease states. For example, for younger patients, I would typically start with a higher dosage, such as 7.5–10 mg daily. In elderly patients, I would start with 2.5–4 mg daily.

**Question:** How would you monitor this patient? What parameters would you follow and why? How frequently would you collect this information?

**Dr. Nutescu:** If we initiate UFH, we have to monitor aPTTs every 6
hours until we attain a therapeutic level and then every 24 hours thereafter. In addition, her platelet count should be monitored daily during UFH therapy, because of the potential risk of HIT. If an LMWH is initiated, then anti-Xa activity monitoring may be considered. Platelet counts must be monitored between days 3 and 5 and every few days thereafter. In addition, she should be monitored for signs and symptoms of bleeding, drug interactions, and daily INRs during hospitalization once warfarin is initiated.

Dr. Haines: In addition, I would be closely monitoring the patient’s symptoms and evidence of disease progression. We may need to use a thrombolytic. Key parameters would include blood pressure, respiratory rate, and arterial blood gases.

Question: Why would you use the aPTT instead of an anti-factor Xa assay to monitor UFH?

Dr. Haines: Frankly, we could use either test. The aPTT is more readily available in most hospitals. The data correlating outcomes to either the aPTT or anti-Xa assay are not strong. The therapeutic range for the aPTT is based on animal data. It is comforting that we have 50 years of accumulated experience, but the proof for justifying the therapeutic range is really quite weak. Some hospitals use the anti-Xa assay to monitor UFH, and that is perfectly fine; it is probably a better assay, and its results are less variable. In many hospitals, the anti-Xa assay is not routinely available, and it may take too long to get the results. And it is more costly.

Dr. Nutescu: I agree. Anti-Xa activity would be a more accurate measure than aPTT to assess heparin anticoagulation. However, this test is not very economical. Our laboratory decided against using it because of the higher cost to run the test. From an accuracy perspective, however, it would be preferred over the aPTT. Many hospitals will not use it because of higher costs.

Question: Assuming that this patient survives the acute event, when would you discharge her?

Dr. Haines: Generally, we would overlap warfarin and heparin therapy for at least five days and continue until a therapeutic INR was achieved. As I have stated, I would use i.v. UFH, which would require that she remain hospitalized for at least five days. Alternatively, if the patient is clinically stable after two or three days of UFH therapy and the INR has increased a bit (e.g., greater than 1.4), I would consider switching her to a LMWH, with the intent of sending her home. This would be particularly true if I worked in a managed care environment where there are strong economic pressures to discharge patients as early as possible. The only reason to keep this patient in the hospital is to continue to monitor her clinical response, as well as her aPTT and INR, more closely than we could in the outpatient setting. While I have a high degree of comfort treating a patient with a DVT in the outpatient setting, we simply do not have a lot of experience treating patients with a PE at home. However, if the patient expressed a strong desire to go home, was clinically stable, and was willing to administer self-injections, I would consider discharging her anytime after the third hospital day, with scheduled follow-up every two to three days thereafter.

Dr. Nutescu: I agree. Once the patient is clinically stable, she could be discharged home.

Question: What regimen would you recommend at the time of discharge, and how long would you recommend anticoagulation therapy be continued?

Dr. Nutescu: Warfarin with an INR goal of 2.5 (range, 2.0–3.0) is the recommended outpatient anticoagulant for this patient, assuming that she does not have an underlying malignancy, in which case an LMWH may be preferred. It appears that this is the first documented thrombotic event for this patient, and no actual cause of this event can be identified. Therefore, this can be considered an idiopathic event. Current guidelines recommend treatment for a first-time acute PE for a minimum of six months. However, two recent studies clearly demonstrate that extending prophylaxis beyond the initial six months of therapy is beneficial. The PREVENT trial randomized patients with a first idiopathic VTE after an initial course of standard therapy for three to six months to low-intensity warfarin (INR goal of 1.5–2.0) therapy or placebo. The study was terminated prematurely due to a 64% reduction in the risk of recurrent events in patients who received warfarin ($p < 0.001$). The second study, ELATE (Extended Low-Intensity Anticoagulation for Unprovoked Venous Thromboembolism), randomized patients with idiopathic VTE after an initial three- to six-month course of standard therapy to either low-intensity warfarin (INR goal of 1.5–1.9) therapy or standard-intensity warfarin (INR goal of 2.0–3.0). The average duration of follow-up was 2.4 years, and patients who received standard-intensity warfarin (INR goal of 2.0–3.0) had a significantly lower rate of recurrent events than the low-intensity group. There was no difference in bleeding complications between groups in either study. I would treat this patient for a minimum of six months with warfarin (INR goal of 2.0–3.0). After the initial six months of therapy, I would reevaluate her to see whether she would benefit from extended prophylaxis. There is a high likelihood that this patient has an underlying hypercoagulable state. If this is documented, the duration of prophylaxis should clearly be extended.

Dr. Haines: I would probably treat this patient for six months. I hesitate to classify this patient’s event as an idiopathic VTE. I would at-
tribute her initial event to estrogen therapy. PREVENT and the ELATE trial do not tell us how many patients had a DVT that was attributable to estrogen therapy or if such events were considered idiopathic. Therefore, these trials do not provide us with clear information about how to manage these patients. I cannot dismiss the possibility that there may be some underlying hypercoagulable disorder combined with the estrogen use in this case. Indeed, many patients who develop a DVT while taking estrogen therapy are later discovered to have an underlying disorder of hypercoagulability. Therefore, I would hesitate to recommend treating this patient for more than six months unless a specific hypercoagulable state was detected during the workup. Now, if after six months of treatment the patient had a significant fear of having a recurrent PE and she really wanted to continue warfarin therapy, I would offer it. If she would develop a second VTE, she most likely has an underlying hypercoagulable disorder. At that point—no question—I would recommend lifelong therapy.

*Question:* Would you recommend continuing all the medications this patient was taking before hospital admission? If not, what alternatives would you recommend?

*Dr. Haines:* This patient was taking lisinopril, rosiglitazone, aspirin, and conjugated estrogens. First and foremost, I would discontinue the conjugated estrogens because I think it was a major contributing factor to the PE. She is 56 years old, and it is not clear why she was taking conjugated estrogens. I assume that it was for postmenopausal symptoms, such as hot flashes. If that is the case, I would recommend an alternative therapy for her symptoms, such as a nonhormonal treatment to control them, if the patient felt they were intolerable. Black cohosh is a possibility because it is relatively inexpensive, and she can purchase it without a prescription. But the safety of black cohosh in patients with a history of VTE has never been examined. So I would lean toward something like venlafaxine because there are data regarding its use in patients with breast cancer who have contraindications to estrogen use. If she was using the estrogens for osteoporosis prevention, I would recommend calcium and vitamin D supplementation.

I would strongly recommend that she continue lisinopril after hospital discharge. She has diabetes, and may have chronic kidney disease, so there are compelling indications for using an angiotensin-converting-enzyme inhibitor.

A more difficult question to answer is, Should we continue aspirin, given that she will be taking warfarin for at least the next six months? While the risk of major bleeding, particularly gastrointestinal bleeding, is higher when the two drugs are used concurrently, she has strong cardiovascular risk factors (diabetes, hypertension, and obesity, and is postmenopausal), so I would recommend continuing aspirin, particularly if she is a smoker. Many of our patients with strong cardiovascular risk factors use low-dose aspirin concurrently with warfarin. The benefits for this patient probably outweigh the risks.

Lastly, let me address the rosiglitazone. It is clearly an effective treatment for diabetes, but one of its primary adverse effects is lower-extremity edema. That could confuse the picture once she leaves the hospital. If she starts to develop lower-extremity edema, or already has it, is it from the rosiglitazone? Or is it the result of another DVT? Because no one would know with certainty without conducting more tests, which only adds to the cost of care, I would consider alternatives. Unfortunately, metformin is not an option because she has renal dysfunction. Insulin is an option but I do not know if she is ready or willing to take it at this point. A sulfonylurea or acarbose could be used. I would at least explore all of the alternatives. I would not automatically continue or discontinue the rosiglitazone. I would need to know a lot more about how well controlled her diabetes is, whether she regularly self-monitors her blood glucose levels, and other factors before I could make an intelligent recommendation.

*Dr. Nutescu:* I agree. As far as the aspirin, I would continue it—however at a lower dose of 81 mg. An enteric-coated tablet would be preferred.

*Question:* How would you manage this patient after discharge from the hospital? What parameters would you follow and when would you obtain them? What goal INR range would you recommend?

*Dr. Nutescu:* The intensity of INR control would be 2.0–3.0 (goal, 2.5) in this case. Ideally, managing the patient in a systematic fashion, such as with an anticoagulation clinic, would be preferred. If that is not an option, usual medical care is an alternative; however, frequent follow-up and education will be necessary to ensure that she is compliant with therapy. How stable she is and what her INR is at the time of discharge will dictate how frequently we will see the patient after she is sent home. If we already have a good sense of her weekly dose, we can see her within a few days of discharge. If she maintains a stable INR on a consistent weekly dose, then she would come back every week for the first month, then every two to three weeks, and then monthly thereafter. On the other hand, if she is not on a stable weekly dose, we would have to see her within a day or two after discharge. Elements that should be monitored include prothrombin time, INR, signs and symptoms of disease recurrence, signs and symptoms of bleeding, surveillance for drug interactions (including prescription and nonprescription drugs.
and herbal supplements), changes in diet, alcohol use, and adherence to therapy.

**Dr. Haines:** While warfarin therapy is far from ideal, I believe Dr. Nutescu makes an important point. INR testing forces us to have continuity of care with this patient. The need for frequent blood tests has, in some way, helped us improve long-term patient management. Anticoagulation clinics essentially provide ongoing clinical and laboratory monitoring activities, monitor patients’ adherence to therapy, and provide patient education.

**Question:** Do you think this patient is a candidate for self-testing or self-management?

**Dr. Haines:** Portable prothrombin-time monitors have revolutionized the way we manage patients. Many anticoagulation clinics use these point-of-care devices so that the INR is available at the time the provider sees the patient. This greatly facilitates patient management. But can a patient use one of these monitors at home? There are data to support this practice, particularly in patients with atrial fibrillation and mechanical heart valves. In self-testing, the patient performs home testing at prescribed intervals and calls the result into a health professional when then makes a judgment about the warfarin dosage. In self-management, the patient independently makes a decision about the warfarin dosage. In this scenario, patients would have little or no contact with a health care practitioner—they would literally manage their own warfarin therapy. In Europe, self-testing and self-management are relatively common practices. In the United States, these practices are uncommon, primarily due to economic reasons. First, the equipment and supplies are expensive and are not covered by most insurance companies. Furthermore, few insurance companies reimburse for the patient education needed to teach patients how to use the equipment and make appropriate dosing decisions.

I would not recommend either practice for this patient. I do not anticipate that this patient will require long-term warfarin therapy; therefore, the cost of the equipment and investment in patient education would not be worth it. Furthermore, this patient is not yet stabilized on therapy. If after six months we decide to continue therapy indefinitely, I might discuss with the patient the option of self-testing, particularly if she were extremely reliable, relatively stable on warfarin therapy, and had the means to pay for it.

**Dr. Nutescu:** The only patients for whom I would consider self-testing are reliable patients who can be educated on the proper use of the device and have difficulty getting to the clinic, such as those with busy travel schedules. For this patient, self-testing does not seem necessary.

**Question:** When a patient is initially started on warfarin and discharged, the INRs are often unpredictable. If the INR drops below 2.0, even though it has been greater than 2.0 for a few days in the past, how do you manage that patient? Would you start enoxaparin or some other LMWH? Is there a certain time period after the diagnosis of PE that you feel comfortable, if the INR drops below 2.0, when you would simply adjust the warfarin dosage and not use an LMWH?

**Dr. Haines:** The answer depends on several factors. Most importantly, how far below 2.0 is the INR? If the INR is 1.9, 1.8, or 1.7, I would not give an LMWH. It is a judgment call. The next factor to consider is the length of time since the occurrence of the thrombotic event. If it has been only two weeks, I would be aggressive and recommend an LMWH. If it has been four or five months, I would probably recommend against using an LMWH, even if the INR was 1.0. It also depends on whether I believe this patient can give herself an injection. If she has given herself s.c. injections in the past, I would not hesitate recommending an LMWH if the INR was 1.5 or less. If she has never given herself an injection, then I have to make a decision. Do I think she is capable of self-injecting? Do I have the time to teach her how to give injections? Do I recommend readmission to the hospital to put her on i.v. UFH again? Again, this decision would really depend on how long it has been since the acute event. Frankly, we do not have a lot of data to guide our decisions. I do not think anyone knows when it is really necessary.

**Dr. Nutescu:** My greatest concern with a low INR after an acute VTE is within the first month of therapy. Data suggest that the rate of recurrent VTE is highest within the first four weeks after an event. If the INR drops to less than 2.0 within the initial four weeks after the event, I would be more prone to initiate UFH or LMWH therapy. If the INR is 1.8–1.9, given possible fluctuations in laboratory test results, I would probably be less aggressive. If the INR dropped to less than 1.8, I would definitely initiate an injectable anticoagulant. If greater than one month has passed since the event, my decision to initiate an injectable agent will be based on the clinical status of the patient—is she active and moving around? If she is immobile and if there are any other concurrent risk factors, I would be more prone to initiate “bridge” therapy.

**Dr. Haines:** Another factor to consider is whether the patient is taking aspirin. That might make me feel a bit more comfortable when the INR is a little low. I might be less aggressive in starting an LMWH, because the aspirin does provide some protection, and the risk of bleeding would be higher, too.

**An emerging option**

**Moderator:** Now I am going to present some information on a new drug—an oral direct thrombin in-
hibitor, ximelagatran—that is currently being tested in Phase III clinical trials. Ximelagatran may be commercially available within the next year or two. It is a selective, competitive, reversible direct thrombin inhibitor with a small molecular weight. It is a prodrug that is transformed after absorption to its active form, melagatran. Ximelagatran was developed to overcome the low oral bioavailability of the active drug. After oral administration, the peak concentration of melagatran occurs within two hours. The elimination half-life is approximately three to six hours. The drug has a linear dose–plasma-concentration relationship with low interindividual variability that results in a more predictable anticoagulant effect and little variation in patient response. Metabolism occurs in the liver unrelated to the cytochrome P-450 (CYP) isoenzyme system. Over 80% of melagatran is eliminated renally and the amount eliminated correlates with the CLcr.

Phase III clinical trials of ximelagatran include the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) and the Thrombin Inhibitor in Venous Thromboembolism (THRIVE) trials. The SPORTIF trials compared the efficacy of ximelagatran with warfarin for the prevention of stroke in patients with atrial fibrillation. Data indicate that ximelagatran is as effective and safe as warfarin for this indication. However, ximelagatran-treated patients were more likely to have significantly elevated alanine transaminase (ALT) levels during the first six months of treatment. None of the patients developed symptomatic liver disease. The THRIVE trial examined the use of ximelagatran for the treatment of VTE. Ximelagatran was as effective as enoxaparin followed by warfarin for six months for the acute and chronic treatment of DVT with or without PE. Again, there was no significant difference in bleeding or mortality between groups, but a small percentage of patients had significantly increased ALT levels during the first six months of ximelagatran treatment. The THRIVE III trial examined long-term use of ximelagatran for the prevention of recurrent VTE in patients who had previously completed a six-month course of standard treatment with enoxaparin and warfarin.

In this trial, patients treated with ximelagatran had an 84% lower risk of recurrent VTE compared with patients receiving placebo. The rate of bleeding was similar in both groups, but liver function tests were elevated in a small percentage of patients who took ximelagatran.

I would like Dr. Nutescu to consider this new drug and the clinical trial data I have briefly presented. What are your initial thoughts regarding this new drug, and which of its features are most attractive to you?

Dr. Nutescu: Ximelagatran has several features that could make use of this agent more attractive than warfarin. It has a short half-life that allows for a faster onset and offset of effect and potentially eliminates the need for an injectable “bridge” agent when initiating or discontinuing therapy. It can be used in fixed doses without the need for dosage adjustment. It has a linear dose–response relationship, a predictable anticoagulant effect, and a wider therapeutic range, which eliminates the need for routine coagulation monitoring. It is metabolized by non-CYP mechanisms and has a lower potential for clinically significant drug or food interactions. Compared with UFH and LMWHs, it can be given orally and does not place a patient at risk for developing HIT. I understand there are some data available for special populations, and it appears that no dosage adjustments would be necessary for weight, age, or sex. We do have to pay attention to renal function, given that the drug is eliminated renally, and dosage adjustment will likely be required in patients with a CLcr of <30 mL/min.

Question: Let us go back to the original case. Would the availability of this new drug change the way you would manage this patient? What additional data would you need? Is there information missing from the initial case that you consider critical for making a decision about whether to use this agent?

Dr. Haines: I need to know the results of the patient’s most recent liver function tests. Based on the Phase III clinical trial data, liver function testing is going to be an issue, and I would need a recent baseline measurement before starting her on this drug.

Dr. Nutescu: Given the patient’s renal function, ximelagatran would likely be contraindicated. We do not have specific dosing guidelines for this agent in patients with a CLcr of <30 mL/min. Another factor to consider before selecting ximelagatran for this patient is her expected compliance with therapy. This drug has a short half-life and is administered twice daily. Missed doses, especially in patients with an acute VTE, may have a much greater effect on efficacy outcomes than missing one or two doses of warfarin. Therefore, before sending her home on ximelagatran after a short hospital stay, I would have to be certain that she will comply with therapy. As monitoring of anticoagulation effect will not be performed and the patient will not be coming in for routine monitoring, baseline education and periodic follow-up education to ensure continued adherence will be critical.

Dr. Haines: That brings up another point. Does this patient have insurance? It is likely that this new drug is going to be far more expensive than warfarin. If this patient does not have the means to pay for this drug, that will be a major barrier to adherence with therapy.

Question: Does the availability of this new drug change your decision
regarding the need for hospitalization or the use of a thrombolytic in this patient? If so, why?

**Dr. Nutescu:** No, I would still hospitalize her and recommend against using thrombolytic therapy in this patient.

**Question:** Does the availability of this new drug change your initial antithrombotic treatment decision? Would you still use i.v. UFH or an LMWH?

**Dr. Haines:** Ximelagatran has an immediate onset of antithrombotic activity, despite the fact that it is administered orally. So it could be easily used in both the acute and long-term phases of treatment. It is not yet known if the THRIVE trial included a large number of patients with acute PE. I would not feel comfortable using this drug initially for the treatment of PE unless there was a large cohort of patients with PE, at least 200 patients, included in the trial. From safety and efficacy standpoints, I would not have any problems using this drug in place of warfarin for the long-term management of this patient. But I would need to examine the published clinical trial data, paying particularly close attention to how severely ill the patients were and how many patients with PE were included before I would feel comfortable using this drug for acute treatment.

In this particular case, I would also be concerned about bleeding due to accumulation of the drug, because it is eliminated through the kidneys. Perhaps a lower dosage could be used, but, at this point, I do not have any data to know what an appropriate dose is.

**Dr. Nutescu:** I would still use an injectable anticoagulant, either i.v. UFH or an LMWH, in this patient for initial therapy. I agree with Dr. Haines that we need more data on the use of ximelagatran for the initial treatment of patients with acute symptomatic PE. We will need to read the full published report carefully and perhaps a second confirmatory study should be conducted before we can draw firm conclusions about the use of oral ximelagatran in patients with acute PE.

**Question:** Does the availability of this new drug change your decision to use warfarin?

**Dr. Nutescu:** If this patient had normal renal and liver function and if we could ensure that she will be compliant with therapy, I would probably feel comfortable, after the initial five days of an injectable anticoagulant, prescribing oral ximelagatran for the remainder of her therapy. I would prefer ximelagatran to warfarin because of its convenience of administration and less complex monitoring and management requirements. However, given this patient’s poor renal function, this would probably be a contraindication to the use of this drug.

**Dr. Haines:** Assuming the patient did not have a contraindication to ximelagatran, I would probably let the patient make the decision. I would tell her that we now have two options for the long-term treatment of PEs. Both options are effective and safe. We have warfarin—a drug that we have 50 years of experience with but requires frequent blood testing to determine the best dosage. Also, it is prone to interactions with other medications and requires consistency in diet with regard to vitamin K intake. A new drug is available that will not require routine monitoring to determine the right dosage but will still warrant liver function tests. Unlike warfarin, it must be taken twice a day. And it is expensive, or I am assuming it will be. I would also add that we do not know the effectiveness of this new drug in the real world. That is, we know how well it worked in clinical trials, but we do not know how effective and safe ximelagatran is in the average patient who may not have qualified to participate in a clinical trial. Are there hidden issues in terms of tolerability or liver toxicity of which we are not yet aware? Warfarin, on the other hand, does not cause liver toxicity. The bleeding risk, if warfarin is used correctly, is probably equivalent to that posed by this new drug. I would ask the patient to make the choice. I would feel comfortable with either choice and would not encourage or discourage the use of either drug.

**Dr. Nutescu:** I would agree with discussing the choices with the patient and presenting the pros and cons of each option. One thing I would like to stress relates to the terminology we use for ximelagatran’s impact on liver function. At this time, it is not clear whether ALT elevations are an indicator of major hepatic toxicity, as none of the patients in the reported trials were clinically symptomatic. A transient rise in ALT was reported in approximately 6–10% of the patients and returned to baseline levels in the majority of the patients, regardless of whether the drug was continued or discontinued.

At this point, the true clinical implications and the long-term effects of this drug are not well understood. This is an area that we will have to follow closely. The monitoring of liver function tests will likely be required for patients who receive the medication. The exact frequency of this monitoring is currently not known. During the clinical trials, liver function tests were conducted monthly for the first 6 months, every 2 months during months 6–12 of therapy, and periodically thereafter.

**Dr. Haines:** True, in the clinical trials the ALT elevations were benign and reversible. However, I think we all remember troglitazone. It was pulled off the market in 1999 when it became apparent that a small number of patients had severe liver failure and died. I am not suggesting the same sort of problem will occur with ximelagatran. Rare or uncommon events may not occur in clinical trials but when the drug is used by millions.
of patients who are a little different than those who participated in the clinical trials, new or more serious adverse events may occur. I am always cautious when a new drug enters the market. I think we all need to be aware that there may be some adverse consequences for a small number of patients that were not observed during the clinical trials.

**Question:** If you and the patient decide to use ximelagatran, how would you monitor therapy? What parameters would you follow and how frequently would you obtain this information? Please also discuss the duration of treatment.

**Dr. Nutescu:** If we use ximelagatran, I still believe we need a structured system of follow-up. This patient just had an acute PE, so we need to have some face-to-face contact soon after discharge to determine whether the patient’s symptoms are improving or worsening. We also need to conduct liver function tests. Follow-up communication regarding liver function could take place via telephone. I think some sort of medication adherence monitoring system would also be important, but I do not know how we are going to actually monitor adherence with therapy without some biological marker. I would still recommend six months of therapy.

**Dr. Haines:** If we use ximelagatran, I agree. Systematic management will be required, but I do not know what form or shape it will take. I believe that anticoagulation clinics are well positioned to get involved in managing and educating these patients. The structure will change as follow-up becomes less frequent. However, some degree of contact with these patients will be required. Perhaps a structure and frequency of visits similar to what we currently use with our patients with dyslipidemia are appropriate. I think we are going to see a shift from a focus on drug monitoring to a focus on thrombotic disease state management.

**Question:** If you used ximelagatran, when would you consider discharging this patient from the hospital, and how would you make that decision?

**Dr. Nutescu:** As discussed previously, she will be transitioned from an injectable anticoagulant to an oral agent. Once she is clinically stable, she can be safely discharged home.

**Question:** I have had a lot of patients asking me about ximelagatran. As a pharmacist with 25 years of experience, I would wait a couple of years before recommending it. Many “wonder” drugs have entered the market for a couple of months, and a few people start having some really serious effects from them. Personally, I would tell patients to take warfarin first unless there was a really compelling reason why they could not take it. What do you think?

**Dr. Haines:** Personally, I am not a risk taker in terms of new medications. I would rather put up with the blood tests every few weeks and watch the foods I eat. I know what drugs to avoid. Taking warfarin would not be particularly difficult for me. I work on an academic health science campus and I can get an INR done at any time. But most patients do not have a well-managed anticoagulation clinic available to them and easy access to getting their blood tests done. Some patients worry about drug interactions or have difficulty monitoring their intake of foods rich in vitamin K. These concerns may be very significant, and deciding which option is best is a value judgment. In the absence of some medical contraindication, the decision to use warfarin or ximelagatran is ultimately the patient’s.

**References**

18. Sanderink GJ, Guimart CG, Ozoux ML et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enox-
Appendix—Risk factors for venous thrombosis

History of deep vein thrombosis or pulmonary embolism
Age > 40 years
Major surgery
Major trauma
Malignancy or prolonged immobility (>4 days)
Major medical illness (congestive heart failure, myocardial infarction, sepsis)
Antithrombin deficiency
Protein C or S deficiency
Activated protein C resistance or factor V Leiden Factor VIII or factor XI (>90th percentile)
Prothrombin (20210) gene mutation
Antiphospholipid antibodies
Heparin-induced thrombocytopenia
Use of estrogen, raloxifene, or tamoxifen