

# CONTINUING EDUCATION



The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education

**ACPE # 012-999-06-167-H01**

**This lesson is no longer valid for CE credit after 10/31/08.**

**An ongoing CE program  
of The University of Florida College of Pharmacy  
and **DRUG TOPICS****

## **Anticoagulation advances: Outpatient treatment of venous thrombosis**

---

To obtain immediate CE credit, take the test on-line at [www.drugtopics.com](http://www.drugtopics.com). Just click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site.

Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits.

# Anticoagulation advances: Outpatient treatment of venous thrombosis

Valerie Prince, Pharm.D., BCPS, FAPhA  
Samford University McWhorter School of Pharmacy

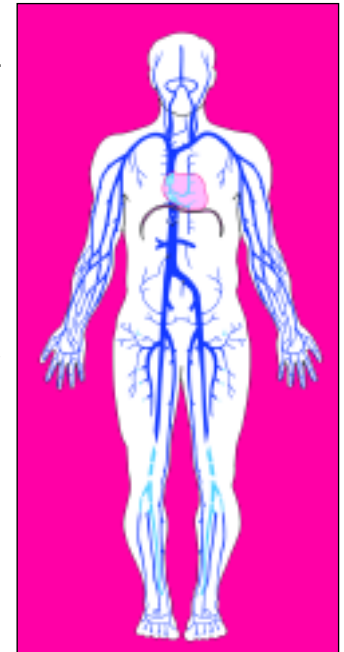
In today's healthcare system, many conditions that would have been treated in the inpatient setting a few years ago are now being managed in the ambulatory setting. Such is the case with the management of uncomplicated venous thromboembolism. Due to advances in our knowledge of anti-coagulation, expensive inpatient hospital stays are often avoided. In some circumstances, the length of a hospitalization can be decreased or the hospitalization can be avoided completely due to our new understanding of safe and effective ways to anticoagulate outpatients.

*Venous thromboembolism* is a term that encompasses both deep vein thrombosis and pulmonary embolism. Deep vein thrombosis (DVT) is a partial or total thrombotic occlusion of the deep venous system of the legs. A thrombus is a fibrin blood clot. If part of the thrombus breaks off and travels to the heart, lungs, or other part of the vascular system, it is termed an *embolus*. Thrombus formation is inhibited by rapid blood flow and facilitated by slower flow. Conditions that allow blood to pool in the legs instead of flowing back to the heart and lungs reduce the clearance and dilution of activated clotting fac-

tors, leading to thrombosis.

Risk factors for DVT include immobility, surgery, malignancy, smoking, pregnancy, oral contraceptive use, older age, major medical illness resulting in venous stasis, and coagulation disorders. The principal cause of pulmonary embolism is DVT.

Symptoms of DVT can include leg swelling, pain, warmth, and erythema. Signs that may be observed are a palpable cord in the patient's affected leg, or a positive Homan's sign (pain in back of the knee upon dorsiflexion of the foot). Signs and symptoms of PE can include shortness of breath, chest pain or tightness, cough, palpitations, tachypnea, tachycardia, neck-vein distension, diaphoresis, or



### GOAL

**For pharmacists to learn the basic concepts of managing drug therapy for patients suffering from venous thrombosis and who require anticoagulation therapy**

### CREDIT

This lesson provides two hours of CE credit and requires a passing grade of 70%.\*

### OBJECTIVES

Upon completion of this article, the pharmacist should be able to:

- ✓ **Describe risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE)**
- ✓ **Discuss appropriate methods to initiate acute and long-term anticoagulation in patients with DVT**
- ✓ **Describe the manifestations of heparin-induced thrombocytopenia and appropriate actions to take when this adverse effect occurs**
- ✓ **Define patient populations for whom outpatient management of DVT is appropriate**
- ✓ **List components of counseling appropriate for patients who require long-term anticoagulation with warfarin and/or low molecular weight heparin (LMWH)**

\*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

hypotension.

The term *proximal DVT* refers to an occlusion in the vessels above the knee. Isolated calf-vein thrombosis is a thrombotic occlusion that is confined to the deep veins in the calf and does not affect the veins above the knee. *Pulmonary embolism* is partial or total thromboembolic occlusion of the pulmonary arteries. *Post-thrombotic syndrome* is a complication of DVT that causes chronic leg discomfort, edema, ulceration, and impaired viability of the subcutaneous tissues of the leg.

One-third of patients with DVT will experience post-thrombotic syndrome within five years. Recurrence refers to another thromboembolic event that occurs after initial partial, total, symptomatic improvement from a thromboembolic event. *Extension* refers to a new constant symptomatic intraluminal filling defect extending from an existing thrombosis. The goal of treating DVT is to prevent recurrence, extension, or adverse effects such as post-thrombotic syndrome or pulmonary embolism, which commonly leads to death.

### Initial management of deep vein thrombosis

Acute DVT of the leg is treated primarily with anticoagulation. The three recommended options for initiating anticoagulation therapy in a patient with a DVT are low molecular weight heparins (LMWHs), IV unfractionated heparin (UFH), and subcutaneous (SC) unfractionated heparin.

The most common treatment approach is to initiate therapy with unfractionated heparin or LMWH when a DVT is suspected or confirmed and initiate warfarin for long-term management. Randomized clinical trials in patients with proximal DVT have shown that it is not necessary to continue heparin for longer than five to seven days once warfarin anticoagulation is at the proper level. Treatment is not initiated with warfarin alone, because patients have a threefold higher rate of recurrent DVT when warfarin is used as

monotherapy.

Until recently, UFH has been the preferred initial treatment of DVT. Unfractionated heparin forms a complex with antithrombin, which inhibits the activity of several clotting factors such as factors IXa, Xa, XIIa, and thrombin. Unfractionated heparin prevents the extension of an existing thrombus and allows the body's own thrombolytic system to degrade the clot.

UFH has an unpredictable dose/response relationship resulting in considerable intra- and interpatient variability in anticoagulation response. UFH binds extensively to a number of substances in the body, including plasma proteins, macrophages, fibrinogen, lipoproteins, and endothelial cells. Patients with active thrombosis have rapid changes in the circulating levels of heparin-binding proteins and may require high doses of heparin to achieve a therapeutic response. UFH is usually monitored via activated partial thromboplastin time (aPTT) measurements—a global anticoagulation test that does not always correlate reliably with the antithrombotic effect of heparin. Subcutaneous (SC) administration of UFH administered twice daily is safe and effective, provided that an adequate starting dose is administered and that this is followed by subsequent doses adequate to maintain a therapeutic aPTT. When patients are receiving subcuta-

## Table 1 Subcutaneous injection technique

Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30- and 40-mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.
- Inject using standard technique, pushing the plunger to the bottom of the syringe.
- Remove the syringe from the injection site, keeping your finger on the plunger rod.
- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.
- Immediately dispose of the syringe in the nearest sharps container.

Source: Lovenox package insert

neous heparin, the aPTT should be drawn six hours after the morning administration, and the dose adjusted to maintain a therapeutic range of 1.5-2.5 prolongation. Bioavailability of UFH administered SC is variable and less than IV heparin administration; therefore, it is common to see an increase in dosing requirements if a patient is changed from IV to SC heparin administration.

LMWHs such as dalteparin, tinzaparin, and enoxaparin also produce their major anticoagulant effect by activating antithrombin. LMWHs have more anti-Xa activity than anti-IIa activity. Anti-factor IIa activity is responsible for the change in the aPTT value used for monitoring UFH. Routine aPTT value monitoring is not necessary in LMWH because of the limited impact the agents have on anti-factor IIa. LMWHs do not bind to macrophages and endothelium to the same degree as UFH. This lesser degree of binding extends the half-life of LMWH as compared with UFH and makes it more predictable, allowing for once- or twice-daily dosing.

## Heparin monitoring and adverse effects

Another advantage of LMWHs is the excellent bioavailability these agents exhibit with SC administration. LMWHs have a more predictable dose/response relationship than UFH and they require less

monitoring. Body weight-adjusted doses of LMWH can be given to most patients once or twice a day without the need for aPTT monitoring. In certain clinical situations, such as renal insufficiency or obesity (>150 kg), it may be advisable to adjust the dose of LMWH based on monitoring plasma anti-Xa levels. Anti-Xa levels should be collected around four hours after SC administration of LMWH. If the LMWH is being dosed twice daily, the anti-factor Xa level should be 0.6-1 IU/ml. If the LMWH is dosed once daily, an anti-Xa level of 1-2 IU/ml is reasonable.

The primary adverse effect of heparin therapy is bleeding. Risk factors for heparin-induced bleeding include the following: increased dose, thrombolytic therapy, glycoprotein IIb/IIIa inhibitor therapy, recent surgery, trauma, or invasive procedures or concomitant hemostatic defect. Heparin used for extended periods of time at high doses has been associated with osteoporosis. Heparin at high doses suppresses osteoblast formation and activates osteoclasts, promoting bone loss. This adverse effect occurs more commonly with UFH than with LMWH therapy. A less common adverse effect of heparin use is hyperkalemia induced by suppression of aldosterone.

Thrombocytopenia is a clinically important side effect of heparin use. Thrombocytopenia may present in two distinct forms in patients receiving heparin therapy. Type I thrombocytopenia is sometimes termed heparin-associated thrombocytopenia but may also be referred to as heparin-induced thrombocytopenia (HIT).

Type I HIT occurs very early in the course of therapy and does not necessitate discontinuation of the heparin therapy. The total decrease in platelet count is less than 50% from baseline and/or the level does not fall less than 100,000. HIT is more common with UFH, but it can

**Table 2**  
**Products high in vitamin K content**

Beef liver	Pork liver	Turnip greens
Broccoli	Kale	Brussels sprouts
Spinach	Chickpeas	Green tea
Chewing tobacco		

occur with LMWH as well. If a patient experiences Type I HIT while on UFH therapy, it would be reasonable to continue the UFH therapy and monitor or, alternatively, to switch the patient to LMWH.

Type II HIT is much more severe and poses a serious threat to the patient's health. Type II HIT is antibody mediated and is associated with venous and arterial thrombosis. Platelet counts commonly fall

below 100,000 or a greater than 50% reduction in baseline in Type II HIT. Type II HIT commonly occurs between days five and 14 of heparin therapy, except in patients with recent exposure to heparin who may have a faster onset.

The risk of HIT varies in different patient populations and with different forms of heparin. The 2004 American College of Chest Physicians (ACCP) *Guidelines on Antithrombotic and Thrombolytic Therapy* directly addresses the issue of HIT and offers guidelines for platelet monitoring and management of HIT if it occurs. Patients who are receiving full-dose UFH should have platelets monitored every other day until day 14 or until heparin is stopped according to the ACCP guidelines. The incidence of HIT is estimated to be about 1% in these patients. Patients on LMWH full therapeutic dose who have received no UFH, however, have a closer to 0.1% incidence of HIT and therefore no routine platelet count monitoring is recommended.

If Type II HIT occurs, ACCP recommendations state that an alternative anticoagulant source should be used. Lepirudin, argatroban, and bivalirudin are all direct thrombin inhibitors named in the guidelines as alternative agents in patients who have HIT with thrombosis. Treatment of HIT-associated DVT with warfarin alone can further complicate the patient's condition. Warfarin monotherapy in HIT-induced DVT can contribute to venous limb gangrene. ACCP recommends

withholding warfarin therapy until the platelet count is substantially recovered (>100,000 minimal).

Some of the direct thrombin inhibitors can prolong the international normalized ratio (INR), which complicates assessing adequacy of the warfarin dose. According to the 2004 ACCP guidelines, warfarin should be initiated in this circumstance at a dose of no more than 5 mg—and the alternative anticoagulant should not be stopped until the platelet count has reached a stable plateau and the INR has been within the target therapeutic range for at least the past two days. For patients who are already on warfarin at the time of diagnosis of HIT, vitamin K 5-10 mg should be used to reverse the warfarin-induced anticoagulation. LMWH should not be used in a patient with HIT, whether or not it is associated with thrombosis.

Fondaparinux is another agent that can be used in the treatment of DVT. Fondaparinux selectively inhibits factor Xa activity. It binds specifically to antithrombin in a reversible manner. It is contraindicated in patients with severe renal function creatinine clearance <30 ml/min. The anticoagulant effects persist after discontinuation of the drug for up to four days. Fondaparinux is administered subcutaneously once a day similar to LMWHs.

### Anticoagulation with warfarin

Warfarin is an oral anticoagulant that acts as a vitamin K antagonist. Vitamin K is necessary in the synthesis of clotting factors II, VII, IX, and X. It is also essential for the synthesis of the natural anticoagulants protein C and protein S. The onset of anticoagulation with warfarin is not immediate, due to its mechanism of action. Existing clotting factors II, VII, IX, and X must be depleted before the full anticoagulant effects of a single dose will be real-

ized.

The rate of depletion of clotting factors is dependent on the half-life of the individual factor. Factor VII has a short half-life of less than eight hours and is therefore depleted within a day, allowing an initial partial response to warfarin to be measured after a single dose. Conversely, factor II has a two- to three-day half-life, and the other factor half-lives lie somewhere in the middle of this range. It typically takes five to seven days after initiation of warfarin or a dose change for the drug effect to reach steady state. The intensity of anticoagulation achieved by warfarin is monitored via measurement of prothrombin time (PT) and is reported as the international normalized ratio. The PT is a measurement of how many seconds it takes a clot to form from a sample of the patient's blood. Reagents are used to perform the test, and different reagents can result in different values being reported from the same sample. To account for the differences in reagents, a standardization system was developed. Each reagent is assigned a sensitivity rating, and that value can be plugged into an equation with the PT value to calculate the INR. Literature recommendations concerning the appropriate therapeutic degree of intensity of anticoagulation are listed in terms of goal INR values.

The primary adverse effect of oral anticoagulation is bleeding. Oral anticoagulation for DVT is associated with a 2% annual risk of a major hemorrhagic event. Risk factors associated with major bleeding in anticoagulated patients include age >65 years, concurrent antiplatelet or NSAID use, history of GI bleeding, falls, heavy alcohol use, renal failure, and cerebrovascular disease.

Pharmacists can help patients maximize the therapeutic effects of long-term warfarin therapy while minimizing the toxic effects. Pharmacists can counsel patients on a number

**Table 3**

### Factors that increase INR values

Congestive heart failure exacerbation  
Hepatic dysfunction  
Hyperthyroidism  
Binge alcohol consumption

## CONTINUING EDUCATION

of elements of safe and effective warfarin use, including dietary considerations and use of OTC and herbal products. Pharmacists should advise patients that the amount of vitamin K-containing foods in their diet will affect their warfarin therapy. Patients should be reassured that it is usually not necessary to eliminate all vitamin K-containing foods from their diet. The key concept for pharmacists to emphasize to patients concerning ingestion of vitamin K-containing foods is consistency. Patients should attempt to maintain a consistent level of vitamin K intake from week to week. It is helpful for the pharmacist to provide examples, preferably through written materials, of foods that are high in vitamin K. One method some pharmacists use when counseling patients on vitamin K intake is to ask patients to make a rule for themselves about the number of vitamin K-containing servings that they will eat each week. Then patients are instructed to be sure to eat the same numbers of servings each week. It is important for patients to understand that eating more vitamin K than usual makes the INR go down, and therefore the patient is more susceptible to clotting. If a sudden decrease in vitamin K intake occurs, the INR may be prolonged and the patient is at additional risk for bleeding.

### ACCP guidelines for management of DVT

The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy report published in 2004 provides clear recommendations for the pharmacological management of DVT and PE. The following are some of these recommendations:

- For acute DVT, treat with UFH or LMWH for at least five days.

**Table 4**  
**Anticoagulant names**

Generic	Brand
warfarin	Coumadin
enoxaparin	Lovenox
tinzaparin	Innohep
dalteparin	Fragmin
fondaparinux	Arixtra
bivalirudin	Angiomax
lepirudin	Refludan

•Initiate warfarin concurrently with LMWH or UFH on the first treatment day and discontinue heparin use when the INR is stable and greater than 2.

•To treat acute DVT, use LMWH once or twice daily over UFH as an outpatient, if possible, and as an inpatient, if necessary.

•Routine monitoring of anti-factor Xa levels is not recommended in patients receiving LMWH for treatment of acute DVT.

•In severe renal failure, IV UFH should be used over LMWH.

It is critically important for patients with DVT to adhere to the five-day overlap in

heparin therapy recommended by the ACCP. Warfarin's vitamin K antagonism not only affects several procoagulant factors (clotting factors II, VII, IX, and X) but also diminishes the presence of the natural anticoagulant protein C. Protein C has a half-life of approximately nine hours, and its synthesis can be diminished so rapidly in some patients in comparison to the decreased levels of clotting factors that the patient is left in an effective hypercoagulable state for a few days. It is important for heparin to be on board in the patient to compensate for this fact.

Patients with acute DVT have a high frequency (15% to 50%) of symptomatic extension of thrombosis and/or recurrent venous thromboembolic events when they are not anticoagulated for a sufficient duration. The drug of choice for long-term anticoagulation in a DVT patient is warfarin. A small minority of patients in whom warfarin is contraindicated (e.g., pregnancy) may be candidates for LMWH or adjusted-dose SC UFH. LMWHs have been shown to be more effective and safer in cancer patients for long-term anticoagulation of DVT. The duration of anti-coagulation varies with the clinical

## CONTINUING EDUCATION

scenario.

Patients were divided into five subgroups for purposes of assigning recommended durations of therapy in the latest ACCP guidelines.

- The first group was made up of patients who experience a first-time DVT due to a known reversible risk factor. A three-month duration of therapy is recommended for this group.
- The second group comprises patients with a first-episode idiopathic DVT (no known cause). Indefinite therapy should be considered in these patients.
- The third group consists of cancer patients with DVTs. These patients should receive LMWH for three to six months, and indefinite anticoagulation should be considered unless they become cancer free.
- The fourth group of patients includes those with underlying coagulation defects (presence of anti-phospholipid antibodies, factor V Leiden and prothombin 20210 gene mutations, etc.). This group should receive a minimum six- to 12-month duration of therapy and possibly indefinite therapy, depending on the exact coagulation defect involved.
- In the last group are patients who have recurrent DVT. Indefinite therapy is recommended for these patients.

The intensity of anticoagulation is also very important in the management of DVT. The target INR range for management of DVT is 2 to 3. Low-intensity anticoagulation (INR 1.5-1.9) has been shown to be less effective and to carry the same risk of bleeding as INR range of 2 to 3. High-intensity anticoagulation (3.1 to 4) has not been shown to be more effective but has been shown to be associated with a high risk (20%) of clinically important bleeding.

### Outpatient management of DVT

The most current ACCP recommendations on anti-coagulation

specifically address the issue of home vs. inpatient treatment of DVT. Several cohort studies reviewed in determining these recommendations supported the safety and efficacy of outpatient treatment of DVT; the studies support the premise that replacing inpatient UFH treatment with outpatient LMWH treatment of DVTs will result in cost savings and improved quality of life.

The American Academy of Home Care Physicians has developed several tools to help clinicians in the identification and management of patients for whom outpatient therapy of DVT and stable PE are appropriate. The AAHCP's DVT guidelines include patients who meet the following three criteria:

- Positive diagnosis of DVT
  - Patient stable with no obvious indication of major pulmonary embolism
  - Adequate patient, caregiver, and/or home nursing support exists
- Contraindications to home DVT therapy, according to these guidelines, are as follows:
- History of hemorrhagic cerebrovascular accident
  - Recent bleeding (e.g., hematuria)
  - Bleeding and/or hematological disorder (e.g., coagulopathy, Hb<8.0, thrombocytopenia)
  - Severe uncontrolled hypertension: SBP  $\geq$ 180 or DBP  $\geq$ 110.
  - Renal failure (SCr >3.0 mg/dL) and/or hepatic failure

Pharmacists can play an important role in the outpatient management of DVT through patient counseling. Patients should have a thorough understanding of the specific drug therapy and monitoring requirements associated with outpatient treatment of DVT.

### Case study

The following is a case study that will illustrate some of the important components of patient counseling and monitoring in outpatient DVT therapy.

## Patient or caregiver counseling for DVT

	<u>Yes</u>	<u>No</u>
<b>Medical condition information</b>		
1. Understands what a DVT is	_____	_____
2. Can recognize the symptoms of a DVT	_____	_____
3. Understands the purpose of Lovenox (low molecular weight heparin) injections	_____	_____
4. Understands the purpose of warfarin therapy	_____	_____
5. Can recognize the signs of disease recurrence	_____	_____
<b>Lovenox counseling points</b>		
1. Method and location of administration	_____	_____
2. Dose and schedule	_____	_____
3. Duration of therapy	_____	_____
4. Signs of over-anticoagulation	_____	_____
5. What to do in case of bleeding	_____	_____
6. Missed dose instructions	_____	_____
7. Storage instructions	_____	_____
8. Risks involved with treatment	_____	_____

### Warfarin counseling points

- |                                   |       |       |
|-----------------------------------|-------|-------|
| 1. Food and drug interactions     | _____ | _____ |
| 2. Dose and schedule              | _____ | _____ |
| 3. Duration of therapy            | _____ | _____ |
| 4. Signs of over-anticoagulation  | _____ | _____ |
| 5. What to do in case of bleeding | _____ | _____ |
| 6. Missed dose instructions       | _____ | _____ |
| 7. Risks involved with treatment  | _____ | _____ |

Signature/Date \_\_\_\_\_

© Copyright 2000 American Academy of Home Care Physicians.

Copying for educational purposes permitted; however, no alteration of content may occur without the permission of the AAHCP.

## CONTINUING EDUCATION

---

CP is a 44-year-old white male who presents to the emergency department complaining of left calf pain and swelling. He reports no previous episodes similar to this one and no history of injury to the leg or the rest of his body. He reports that he took an extended coast-to-coast flight home from a business trip the preceding day. His medical history is significant for occasional GERD and sinus headaches. He is 5'11" tall and weighs 87 kg.

An ultrasound confirms that CP has a DVT, and anticoagulation is indicated. CP is given an enoxaparin injection and a dose of warfarin. The emergency room physician gives CP prescriptions for enoxaparin 140 mg daily X 4 days and warfarin 5 mg daily X 10 days. The emergency room physician gives CP instructions to have the prescriptions filled immediately and to contact his primary care provider the next day.

CP shows up at your pharmacy full of questions. How do you address each of his inquiries?

•*How long will I need to take these?* The duration of anticoagulation for DVT is dependent on the cause of the DVT and the presence of other conditions. CP can be told that his physician may run tests to see if there is an underlying cause for his DVT, but if none is found, his DVT can likely be attributed to the long airline flight. Since this is a known reversible risk factor and this is a first-time DVT, his duration of anticoagulation is likely to be three months. He should be told that he probably will be using the injections for a short period of time only, but it is important for him to continue using them until the clinician managing his anticoagulation tells him he can stop.

•*Why do I have to see my doctor so soon, and why did the ED doctor tell me I would probably have to get blood drawn "a lot" for a while?* CP should be told that the injections work immediately to help prevent the clot from getting bigger or breaking loose and traveling to other parts of his body but that the pills work slowly. He should be told that blood tests are necessary to see whether or not the medication has had time to take effect properly. CP should be educated about the terms PT and INR so he will be familiar with them and be aware of how criti-

cally important it is for him to get the labs drawn. The consequences of noncompliance should be explained to him bluntly.

•*What is a "good" INR number for me, and what happens if it isn't right?* CP can be told that his target INR range is 2 to 3. If the number is too low, it means that his blood is "too thick" and that he is at risk for another clot or complications from the existing clot. If the number is too high, it means his blood is "too thin" and he is at risk for bleeding.

•*Will it be a problem for me to take other medicine while I am taking warfarin?* CP should be informed that warfarin is associated with multiple food and drug interactions. He should be counseled to tell anyone who is writing prescriptions for him that he is on warfarin. He should also be warned that many OTC and herbal products (such as garlic and ginkgo) can interact significantly with warfarin to increase his risk for bleeding. He should be advised to avoid self-medication with aspirin or NSAIDs or large daily doses of acetaminophen. With CP's history of occasional GERD, it would be prudent to warn him that omeprazole can interact with warfarin to prolong his INR.

•*Is there anything else I need to know?* CP should be advised to watch for signs of bleeding (blood in the urine or stool, excessive blood when brushing teeth, coughing up blood, etc.). He should also be taught to recognize signs of potential thromboembolism. Many patients would recognize a recurrent DVT because the presentation may be similar to the first episode. Those same patients, however, usually do not understand the symptoms of different thromboembolic presentations without education. CP should be told to be aware that any of the following could be signs of a clot somewhere in his body: Shortness of breath or chest pain; dizziness; unusual confusion; slurred speech; numbness in jaw or face; weakness or paralysis of limbs or one side of the body; acute vision changes; or unusual pain, swelling, or discoloration of the legs. He should be told that if he experiences any of these symptoms, he should contact the clinician managing his anticoagulation therapy immediately, and if he is

## CONTINUING EDUCATION

---

not able to reach that person, he should go to the emergency room.

CP comes in to the pharmacy two weeks later to have a warfarin prescription for a different strength filled. He explains to you that he went to his doctor's office to have blood work done and later a nurse called him and told him his warfarin dose was being decreased. When CP asked the nurse what could have necessitated this decrease in dose, the nurse told him he must have been eating too many "greens." CP tells you he hates green leafy vegetables and that he has been very careful to eat a consistent amount of high vitamin K-containing foods while he has been on warfarin therapy. CP asks you what could have made his blood "too thin"? What kind of questions do you ask him to discover what could have impacted his INR?

First, make sure CP understands that the nurse was incorrect to state that increased consumption of greens can cause a dose reduction. CP should be questioned about recent use of over-the-counter drugs, including herbal medications. If he reports use of any OTCs, try to elicit details of how much he took a day and for how long. Some products (such as acetaminophen) that are harmless in smaller doses can be a problem in larger doses for a patient on warfarin. Ask if CP missed any doses, and, if so, did he "double up" doses within a few days of having his INR drawn. Review the medication profile you have for CP and make sure he didn't get a new prescription medication filled at another pharmacy. Review CP's medical history and make sure he has no new diagnosis such as heart failure or hepatic disease that would affect the INR. Ask CP also about alcohol ingestion. Explain to him that acute alcohol ingestion often results in elevated INRs but that chronic alcohol ingestion usually results in a decreased INR.

CP comes into your pharmacy two weeks later with a prescription for double-strength sulfamethoxazole/ trimethoprim (SMZ-TMP) for treatment of a sinus infection. How will this impact his anticoagulation therapy?

SMZ-TMP has a clinically significant drug interaction with warfarin. SMZ-TMP inhibits the metabolism of the most active isomer of warfarin via inhibition of the CYP2C9 hepatic enzyme system, and it can result in a pronounced extension of the INR. The onset of the interaction is typically several days. Some clinicians may choose to empirically alter the warfarin dose when SMZ-TMP therapy begins; others wait until the extent of the INR prolongation is determined. It is not contraindicated to use SMZ-TMP with warfarin, but it does require increased INR monitoring. CP should be reminded to watch for signs of bleeding and be sure he has his INR drawn as instructed. It would be appropriate for the pharmacist to ask the patient if the clinician who prescribed the SMZ-TMP knew about the warfarin when the prescription was written. If the sulfa-prescribing clinician is not the same as the clinician monitoring the anticoagulation, the pharmacist should advise CP to contact his anticoagulation clinician with the news that he has started SMZ-TMP therapy.

CP comes back to your pharmacy four days later to pick up guaifenesin. He is afraid his sinus infection has progressed to pneumonia because he has been coughing hard and has even "spit up some blood" this morning. He tells you he is very anxious about this and that it is making his heart race and his chest feel tight. It is Friday night and he asks you if you think he should wait until Monday to see his regular doctor or if he should go to a "doc-in-the-box" in the morning. What do you tell him?

Forget the "doc-in-the-box." CP needs to go to the emergency department immediately. Although the symptoms he describes could be caused by pneumonia and anxiety, they could also be caused by a pulmonary embolism, which is a life-threatening complication of a DVT. Hemoptysis could also indicate that CP is experiencing a bleeding complication of over-anticoagulation resulting from the drug interaction with his antibiotic.

*References are available upon request.*

# TEST QUESTIONS

Mark the most appropriate answer. The answer form follows the test questions.

1. Which of the following is *not* a sign of thromboembolism?
  - a. Tachycardia
  - b. Diaphoresis
  - c. Hypotension
  - d. Hematochezia
2. The principal cause of pulmonary embolism is:
  - a. Pneumonia
  - b. Stroke
  - c. Coronary artery disease
  - d. Deep vein thrombosis (DVT)
3. The complication of DVT that causes chronic leg discomfort, edema, and ulceration of the leg is:
  - a. Post-thrombotic syndrome
  - b. Peripheral arterial disease
  - c. Thrombosis stasis
  - d. Post-thrombotic necrosis
4. Which of the following is *not* recommended for the initial management of DVT?
  - a. Dalteparin
  - b. Clopidogrel
  - c. Unfractionated heparin IV
  - d. Unfractionated heparin SC
5. Which one of the following labs may be advisable for use in adjusting LMWH doses in patients with renal insufficiency?
  - a. aPTT
  - b. PT
  - c. Anti-Xa
  - d. INR
6. Which of the following statements is *true* concerning Type II heparin-induced thrombocytopenia?
  - a. It is associated with a decrease in platelet count of no more than 25% from baseline.
  - b. It is antibody mediated.
  - c. It usually occurs during the first 24 hours of therapy.
  - d. It does not occur with LMWHs.
7. Which of the following agents is *not* recommended as an alternative anticoagulant in patients who experience heparin-induced thrombocytopenia with thrombosis?
  - a. Abciximab
  - b. Argatroban
  - c. Bivalirudin
  - d. Lepirudin
8. Which of the following actions/statements is part of the ACCP guidelines on the management of HIT-associated DVT?
  - a. Administer vitamin K 5–10 mg to patients who are already on warfarin at the time of diagnosis of HIT.
  - b. Initiate warfarin immediately in patients diagnosed with HIT-induced DVT.
  - c. Direct thrombin inhibitors do not alter INR values.
  - d. Patients on LMWH should have platelet counts monitored every other day until day 14 of therapy.
9. Which one of the following is a natural anticoagulant agent suppressed by warfarin?
  - a. Protein C
  - b. Thrombin
  - c. Thromboxane A<sub>2</sub>
  - d. Factor VII
10. The lab test that measures the number of seconds it takes a clot to form in a sample of the patient's blood is:
  - a. INR
  - b. Prothrombin time
  - c. Activated partial thromboplastin time
  - d. Anti-Xa
11. A steady-state level of warfarin is achieved in how many days in a typical patient?
  - a. One to three days
  - b. Five to seven days
  - c. Two weeks
  - d. One month

## TEST QUESTIONS

---

- 12.** Which one of the following is a risk factor associated with major bleeding in anticoagulated patients?
- Renal failure
  - Heart failure
  - Age 55 to 65
  - History of peripheral vascular disease
- 13.** Which one of the following agents should be used as first-line management of DVTs in most patients, according to the 2004 ACCP guidelines on thrombolytic therapy?
- Alteplase
  - LMWH
  - Two weeks
  - Clopidogrel
- 14.** Which one of the following agents should be used in initial management of DVT in patients with renal failure?
- UFH
  - LMWH
  - Argatroban
  - Clopidogrel
- 15.** How many days of overlapping heparin and warfarin therapy are recommended by the 2004 ACCP guidelines on thrombolytic therapy in the initial management of DVT?
- Two days
  - Five days
  - 10 days
  - 14 days
- 16.** Which agent should be used for long-term anticoagulation in cancer patients with DVT?
- LMWH
  - UFH
  - Warfarin
  - Clopidogrel
- 17.** ACCP recommends what duration of long-term anticoagulation in a patient with a first-episode idiopathic DVT?
- Three months
  - Six months
  - 12 months
  - Indefinite
- 18.** What is the minimum duration of therapy recommended for patients with DVT and underlying coagulation defects?
- Three months
  - Three years
  - Six months
  - Lifetime
- 19.** Which one of the following is *not* a contraindication for home treatment of DVT according to the American Academy of Home Care Physicians?
- Severe uncontrolled hypertension
  - Hepatic failure
  - Pulmonary failure
  - History of hemorrhagic CVA
- 20.** Which one of the following represents the most clinically significant drug interaction with warfarin?
- Sulfamethoxazole/trimethoprim
  - Cephalexin
  - Atenolol
  - Lisinopril

## EVALUATION OF CE

*Drug Topics* is conducting an evaluation of this CE article. Please ✓ box that best reflects your opinion of the evaluation questions. Please keep this evaluation attached to your answer form.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were met.				
2. The program content was useful and relevant.				
3. The program was educational and not promotional.				
4. The program was fair, objective, balanced, and of scientific rigor.				
5. The program will help me in my practice.				

### 2006 CEU CREDIT REQUEST

To obtain immediate CE credit, take the test on-line at [www.drugtopics.com](http://www.drugtopics.com). Just click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site. Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits.

### ANSWER FORM

**Anticoagulation advances: Outpatient treatment of venous thrombosis**

OCTOBER 23, 2006 ACPE # 012-999-06-167-H01

Test questions start on preceding page

- |                |                |                 |                 |                 |
|----------------|----------------|-----------------|-----------------|-----------------|
| 1. a. b. c. d. | 5. a. b. c. d. | 9. a. b. c. d.  | 13. a. b. c. d. | 17. a. b. c. d. |
| 2. a. b. c. d. | 6. a. b. c. d. | 10. a. b. c. d. | 14. a. b. c. d. | 18. a. b. c. d. |
| 3. a. b. c. d. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. c. d. | 19. a. b. c. d. |
| 4. a. b. c. d. | 8. a. b. c. d. | 12. a. b. c. d. | 16. a. b. c. d. | 20. a. b. c. d. |

**Are you employed by a chain?  
If so, which one?**

- Amount enclosed:  \$6.00 for this lesson  
 \$54.00 for any 12 lessons you take over the next year, starting from the date you sign up  
 Already series-enrolled for 2006

**Submit your check (payable to The University of Florida) and form to:**

University of Florida College of Pharmacy, P.O. Box 100482, Gainesville, FL 32610

E-mail address: [continuinged@cop.ufl.edu](mailto:continuinged@cop.ufl.edu)

Fees not refundable or transferable

For questions concerning PRINT CEs, call (352) 273-6275.  
 For questions concerning ON-LINE CEs, call (866) 261-3558.

No longer valid for CE credit after 10/31/08

#### REGISTRANT INFORMATION

**Name:** \_\_\_\_\_  
(Last) (First) (M.I.) Phone

**Address:** \_\_\_\_\_ **E-mail address:** \_\_\_\_\_  
(Street)

**City:** \_\_\_\_\_ **State:** \_\_\_\_\_ **Zip:** \_\_\_\_\_

**ATTENTION FLORIDA PHARMACISTS:** The State of Florida has changed to a new record maintenance system for all continuing education, using a private company, [cebroker.com](http://cebroker.com). The University of Florida is registered with the Florida Board of Pharmacy as a Provider, and will report continuing education records for all pharmacists who are registered in Florida.

Please provide your license number \_\_\_\_\_