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Treating DVT: Answers to 7 key questions

Complex recommendations for anticoagulant therapy raise questions for family physicians. Here are the evidence-based answers you need to manage DVT patients successfully.

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PRACTICE RECOMMENDATIONS

- *Start patients with a new-onset venous thrombosis on a low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux as well as warfarin therapy.* (A)
- *Continue LMWH, UFH, or fondaparinux with warfarin for a minimum of 5 days until the international normalized ratio (INR) is ≥2 for 24 hours.* (A)
- *Educate patients about anticoagulant therapy, dietary and medication interactions with warfarin, and signs and symptoms of bleeding.* (A)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Arterial and venous thromboses are major causes of morbidity and mortality in the United States. Each year, about 100 out of 100,000 Americans (0.1%) experience a venous thromboembolism (VTE), and the incidence is considerably higher among hospitalized patients.[1] Incidence and early mortality after a first-time event increase with age. Mortality and the potential for a pulmonary embolism (PE) to occur after a deep vein thrombosis (DVT) depend on the location of the DVT and how well the DVT is managed. Proximal DVTs are more likely to develop into a PE. Mortality rates for patients with PE are as high as 17% 3 months after diagnosis.[2]

Anticoagulant therapy is the foundation for prevention and treatment of thromboembolic disease, and family physicians are on the front line of management when patients with DVT are discharged from the hospital. There are many therapeutic options to choose from: unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), the factor Xa inhibitor fondaparinux, direct thrombin inhibitors, or vitamin K antagonists (VKAs). All of these agents are effective, but you'll need to keep clinical considerations and drug limitations in mind to use them properly.

The salient details for optimal use of these agents are set out in the 8th edition of the American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines, released in 2008.[3] But following these complex guidelines to maximize patient safety and minimize both cost and inconvenience raises many questions for the busy family physician. This article provides the answers you need to maximize your care.

1 What therapies can be used in the outpatient setting to treat acute DVT or PE?

You can manage DVT with LMWH—dalteparin (Frag-

TABLE 1

Low-molecular-weight heparins and fondaparinux dosing for DVT

Agent	Dose
Dalteparin (Fragmin)[21]	100 units/kg SQ every 12 h *or* 200 units/kg SQ every 24 h
Enoxaparin (Lovenox)[22]	1 mg/kg SQ every 12 h *or* 1.5 mg/kg every 24 h
Tinzaparin (Innohep)[23]	175 anti-Xa IU/kg SQ every 24 h
Fondaparinux (Arixtra)[24]	Weight <50 kg: 5 mg SQ every 24 h Weight 50-100 kg: 7.5 mg SQ every 24 h Weight >100 kg: 10 mg SQ every 24 h

DVT, deep vein thrombosis; SQ, subcutaneously.

min), enoxaparin (Lovenox), or tinzaparin (Innohep)—or the factor Xa inhibitor fondaparinux (Arixtra) overlapped with warfarin (Coumadin). UFH is generally not recommended in the outpatient setting. Patients who are obese or have a creatinine clearance <30 mL/min will need inpatient treatment with UFH in most cases.

Outpatient management of PE based on clinical prediction rules that stratify patients by risk factors has been attempted, although the safety and efficacy of this practice have not been conclusively demonstrated. Prediction rules are available at http://www.medicalcriteria.com/criteria/car_thrombosis.htm. Note that LMWH and fondaparinux are not approved by the US Food and Drug Administration (FDA) for the outpatient treatment of PE.

Dosing guidelines for LMWH agents and fondaparinux are given in **TABLE 1**, and recommendations for treatment of DVT are summarized in **TABLE 2**.

2 When, and at what dosage, should I initiate warfarin?

With a medically stable patient, you can start warfarin shortly after the first dose of LMWH or fondaparinux, and overlap both therapies for at least 5 days until the patient's international normalized ratio (INR) is ≥2 for 24 hours. If the INR does not reach 2 within 5 days, LMWH or fondaparinux should be continued. The target INR for DVT is 2.5.

The initial dose of warfarin for most patients should be between 5 and 10 mg per day for the first 2 doses, with 10-mg doses reserved for younger patients without significant drug interactions or comorbidities.[4] Consider a starting dose ≤5 mg in elderly patients, those with certain medical conditions (eg, liver disease or heart failure), and patients taking medications known to significantly inhibit warfarin metabolism.[3,4] **TABLE 3** provides a suggested method for initiation of warfarin in ambulatory patients.

Continue warfarin for at least 3 months, and possibly longer, depending on the cause of DVT/PE and underlying or ongoing risk factors. Evaluate the risk vs benefit of continued therapy 3 months after the initial thromboembolic event. Patients with cancer, whose risk for VTE is greater, should receive LMWH for the first 3 to 6 months, followed by long-term therapy with warfarin or LMWH until the cancer is resolved.[3,4]

3 Is it time to customize anticoagulant therapy based on genetic testing?

No. Currently, FDA and ACCP guidelines do not recommend genetic testing before initiating warfarin.[5,6] Theoretically, genetic testing should be helpful in predicting an individual's optimal starting warfarin dose. At present, however, no good clinical data support this practice.[5] If randomized trials show improved

LMWH and fondaparinux are not approved by the US Food and Drug Administration for the outpatient treatment of PE.

TABLE 2

Treating DVT: Recommended options[3,4,21-24]

Warfarin	UFH	LMWH
Starting dose 5-10 mg/d for first 1-2 days. Lower starting dose for patients with liver impairment, malnourishment, heart failure, or recent major surgery; for debilitated and elderly patients; and for patients on medications known to inhibit CYP-450 enzyme. Initial monitoring after the first 2-3 doses. Maintenance monitoring at least every 4 weeks. For acute DVT, overlap with LMWH, UFH, or fondaparinux for at least 5 days and until INR is ≥2 for 24 hours. Continue therapy for ≥3 months for patients with upper extremity DVT.	UFH is recommended for patients who are obese or have a creatinine clearance <30 mL/min; UFH is generally an inpatient treatment option, and patients may need to be admitted for therapy.	For acute DVT, LMWH daily or twice daily is recommended over UFH. Exceptions include patients who are obese or have a creatinine clearance <30 mL/min. Anti-Factor Xa levels should be monitored in pregnant patients on therapeutic doses of LMWH.

DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

clinical outcomes with pharmacogenetic dosing of warfarin, genotyping may become part of clinical practice in the future.

An estimated one-third of patients on warfarin therapy may be at higher risk for adverse outcomes because they carry genes that make them more or less sensitive to warfarin.[5] Variants of 2 genes—cytochrome P450 2C9 (CYP2C9) and the vitamin K oxide reductase complex 1 (VKORC1)—are thought to be responsible for this variance in warfarin response.[5]

Patients with variations of CYP2C9 may need lower starting doses of warfarin. Mutations in the VKORC1 gene affect the enzymes that activate vitamin K, which are the target for warfarin's inhibitory effect on clotting. Mutations in this gene therefore result in varying sensitivities to warfarin and may be the cause of hereditary warfarin resistance in some individuals. Genetic variations in VKORC1 are estimated to occur in 14% to 37% of Caucasians and African Americans and may exist in as many as 89% of Asians.[5] Several tests to detect some variants in these genes have been approved by the FDA.

In August 2007, a labeling change for Coumadin and its generics detailed the influence of gene variations on warfarin sensitivity.[7] A report from the American Enterprise Institute-Brookings Joint Center for Regulatory Studies estimated that genetic testing could prevent 85,000 serious bleeding events and 17,000 strokes per year, resulting in a $1.1 billion reduction in warfarin-related health care spending. Costs of genetic testing for the 2 million Americans who begin warfarin therapy each year would be approximately $1 billion.[6]

4 Which warfarin–drug interactions are clinically important?

Drugs, supplements, and foods that potentiate or inhibit warfarin's anticoagulant effect or increase the risk of bleeding are clinically important. The list of such interactions has been referred to as the 8 "As": antibiotics, antifungals, antidepressants, antiplatelets, amiodarone, anti-inflammatories, high-dose acetaminophen, and alternative remedies.[8] (For details on common warfarin interactions, see **TABLE W1**, at jfponline.com.)

These and other medications can affect how warfarin is absorbed, distributed, and me-

TABLE 3
Average warfarin daily dosing for INR goal 2-3

	Dosage change	Patients nonsensitive to warfarin	Patients sensitive to warfarin*
Initial dose		5 mg/d	2.5 mg/d
First INR		3 days after initial dose	3 days after initial dose
<1.5	Increase dose by 50%	7.5 mg/d	5 mg/d
1.5-1.9	Maintain current dose	5 mg/d	2.5 mg/d
2-3	Decrease dose by 50%	2.5 mg/d	1.25 mg/d
3.1-4	Decrease dose by ~75%	1.25 mg/d	0.5 mg/d
>4	Hold dose	Hold	Hold
Next INR		2-3 days	2-3 days

INR, international normalized ratio.

*Factors that influence sensitivity to warfarin include age >75 years, clinical congestive heart failure, diarrhea, drug interactions, elevated baseline INR, hyperthyroidism, malignancy, malnutrition, or nothing by mouth for >3 days.

Source: University of Washington Medical Center. Average daily dosing method. Available at: http://vte.son.washington.edu/docs/VTE_flexible_initiation.pdf. Accessed September 26, 2010.

tabolized. For example, sucralfate and bile-acid sequestrants such as cholestyramine can inhibit absorption. You can minimize this interaction by staggering the time each medication is ingested. Drugs that induce cytochrome P450 enzymes (eg, rifampin, carbamazepine) enhance warfarin clearance, while drugs that inhibit CYP enzymes (amiodarone or itraconazole) decrease warfarin clearance.[2] Most clinically relevant interactions affect warfarin metabolism.

5 How should I proceed when a patient taking warfarin also needs antiplatelet medications?

Monitor warfarin more frequently in such patients and target the lower end of the INR therapeutic range (2-2.5).[9] Keep an eye on your patient's overall medication regimen and avoid medications like nonsteroidal anti-inflammatory drugs (NSAIDs) that increase bleeding risk. If NSAIDs must be used, avoid chronic use, high doses, and NSAIDs with a long half-life. You may also want to consider referral to an anticoagulation clinic.

Many of these patients have cardiac conditions for which dual antiplatelet therapy is recommended. For example, patients with coronary stents may need aspirin and clopidogrel for a specified period of time. They may have underlying atrial fibrillation or valve replacement requiring warfarin therapy. Data examining triple therapy (aspirin, clopidogrel, and warfarin) are primarily limited to patients with acute coronary syndrome or those who have had percutaneous coronary intervention. Unfortunately, the data are also retrospective, based on a small sample, and inconsistent.[10] In these patients, you need to weigh the increased risk of bleeding against the proven preventive value of each of these modalities.

For patients with stents, current guidelines recommend a lower dose of aspirin and discontinuation of clopidogrel after a certain length of time, depending on the type of stent.[10,11] However, 1 study showed that aspirin dose and INR values did not influence bleeding risk in patients on triple therapy.[12]

It is imperative that you counsel patients on triple therapy to report the first sign of bleeding.

6 What is the best approach when a patient's INR is elevated?

You'll need to minimize the risk of bleeding while at the same time ensuring adequate levels of anticoagulation. You can use oral vitamin K (phytonadione [Mephyton]) to re-

If NSAIDs must be used, avoid chronic use, high doses, and NSAIDs with a long half-life.

TABLE 4

Managing elevated INR

For any INR above therapeutic range	Monitor more frequently and resume anticoagulation at an appropriately adjusted dose when the INR is at a therapeutic level.
INR above therapeutic range, but ≤5.0 and no significant bleeding	Lower the dose or omit a dose; INR only minimally above therapeutic range or associated with a transient causative factor may not require dose reduction.
INR >5.0 but <9.0, and no significant bleeding	Omit 1 to 2 doses. Alternatively, if the patient is at increased risk of bleeding, omit a dose and administer vitamin K (1-2.5 mg) orally. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (<5 mg orally) will reduce INR within 24 hours. If INR remains high, give additional vitamin K (1-2 mg) orally.
INR ≥9.0	Hold warfarin therapy and administer vitamin K (2.5-5 mg orally); INR will be reduced substantially in 24-48 hours. Administer additional vitamin K if necessary.
Serious bleeding regardless of INR	Hold warfarin and give vitamin K (10 mg by slow IV infusion). May repeat in 12 hours if necessary. Administer FFP, PCC, or rVIIa if necessary.
Life-threatening bleeding	Hold warfarin. Administer vitamin K (10 mg by slow IV infusion). May repeat if necessary. Administer FFP, PCC, or rVIIa along with vitamin K.

FFP, fresh frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate; rVIIa, recombinant factor VIIa.

Adapted from: Ansell J, et al. *Chest*. 2008.[4]

verse the effects of warfarin without inducing warfarin resistance. Avoid subcutaneous administration; the effects are unpredictable and response is delayed.[4]

Send patients with active or life-threatening bleeding to the emergency department. Reserve intravenous vitamin K administration for patients who are bleeding or have an INR >20. The ACCP guidelines provide recommendations on managing elevated INRs in patients receiving warfarin (**TABLE 4**).[4]

7 What new anticoagulants are on the horizon?

Several alternative treatments for DVT are currently in clinical trials, and 1 recently received FDA approval.

Ximelagatran, a direct thrombin inhibitor, appeared to hold promise as an oral anticoagulant, but was denied FDA approval and eventually withdrawn by its manufacturer when reports of hepatotoxicity and possible myocardial ischemia surfaced.[13,14] Other oral treatment options to be aware of include another direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors apixaban and rivaroxaban.

Dabigatran (Pradaxa), an oral direct thrombin inhibitor similar to ximelagatran, received FDA approval last month for stroke prevention in atrial fibrillation. One study, RE-COVER, studied dabigatran vs warfarin for the treatment of acute VTE—both lower extremity DVT and PE. This noninferiority trial compared dabigatran 150 mg twice daily with daily warfarin adjusted to achieve an INR of 2.0 to 3.0, with the 6-month recurrence of VTE as the primary outcome. Dabigatran was found to be as effective as warfarin at preventing recurrent or fatal VTE. There

How would you manage this case of DVT?

Your patient, a 64-year-old man, has a 4-day history of warmth and tenderness in his right calf. Two weeks earlier, he had knee replacement surgery. He left the hospital with a prescription for enoxaparin (Lovenox) 30 mg every 12 hours for 5 days (for a total of 10 doses), but he tells you that he did not get the prescription filled because of the cost. (Even with the copay, it was more than he thought the medication was worth.)

Your clinical diagnosis is a deep vein thrombosis (DVT), and this is confirmed by a venous Doppler ultrasound study showing a clot extending from the popliteal to the femoral vein. He has no signs of a pulmonary embolism (PE), no shortness of breath or chest pain, and according to your office PE prediction calculator, his probability of PE is low. He doesn't want to go back to the hospital for treatment, and you agree that he is capable of managing his condition at home. At a weight of 98 kg, he isn't obese and his serum creatinine and complete blood count are within normal limits.

Q How would you treat this patient?

A

You decide to start the patient on enoxaparin 100 mg subcutaneously every 12 hours. You teach him proper injection technique and write a prescription for 10 syringes with 1 refill. He now understands that the medication is essential and is ready to cover the copay. You also start him on warfarin 5 mg daily. You explain that when he is taking warfarin, he needs to have his blood clotting time tested frequently. He'll need a lab test of his international normalized ratio (INR) on Day 3 and Day 5 of warfarin. If the INR is ≥2 after 5 days, he can stop enoxaparin therapy. If the INR is <2 on Day 5, he will need to continue enoxaparin until the INR is ≥2.

On Day 5, your patient's INR is 2.5, so you tell him to stop taking enoxaparin and continue regular INR testing, getting his next test within 1 week of this office visit. His INR remains stable for 3 months on 5 mg warfarin daily. Then you get a call from the lab, telling you the patient's INR is elevated at 4.2.

Q What could be causing your patient's INR to be elevated?

A

You call the patient and ask if he has been taking his medication faithfully and whether he has been eating normally. You also ask whether he has started any new medications.

He tells you he has been taking his warfarin and hasn't made any changes in his diet, but he is on the last day of a 7-day treatment with metronidazole for pseudomembranous colitis. He says he has had no bleeding and has not noticed any large bruises or dark stools. The elevated INR is probably a drug interaction with the metronidazole. You tell him to skip his warfarin for 1 night and then have his INR rechecked. The next day, the INR is back in the normal range. He continues on warfarin therapy. His INR remains stable and his leg pain does not recur.

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was no difference in major bleeding between the dabigatran and warfarin groups, although the dabigatran group did show more major or clinically relevant nonmajor bleeding. No differences in other adverse events were observed between the 2 groups.[15]

Three studies, RE-MOBILIZE, RE-NOVATE, and RE-MODEL, compared dabigatran's efficacy and safety with enoxaparin for the prevention of VTE after knee and hip replacement surgery. In the RE-MOBILIZE trial, dabigatran was effective

compared with enoxaparin once daily, but not effective compared with twice-daily enoxaparin.[16] The RE-NOVATE and RE-MODEL studies also showed dabigatran's efficacy compared with once-daily enoxaparin.[17-19] Major bleeding occurred in approximately 1% of patients in both the dabigatran and enoxaparin treatment groups, and the incidence of hepatotoxicity was similar.[17-19]

The RE-LY trial studied warfarin vs 2 different doses of dabigatran in atrial fibrillation for the prevention of stroke or systemic embolism. Both doses of dabigatran (110 mg twice daily or 150 mg once daily) were similar to warfarin for the study's primary outcome, and dabigatran at the 110-mg dose had a significantly lower incidence of hemorrhagic stroke.[19] Studies on the use of dabigatran in acute coronary syndrome are ongoing.

Apixaban and rivaroxaban are oral inhibitors of both free and fibrin-bound factor Xa. They are similar in activity to the currently available, injectable fondaparinux. In the RECORD 1, 2, 3, and 4 trials, rivaroxaban was compared with once- or twice-daily enoxaparin in patients undergoing hip and knee replacement surgery.[20] Rivaroxaban was significantly better in preventing VTE and it had a comparable rate of major bleeding (approximately 0.2%). Rivaroxaban has been approved in Canada and Europe for thromboprophylaxis after major orthopedic surgery. Rivaroxaban was recommended for approval by an FDA advisory panel, but the FDA has not issued an approval as yet.

Phase III trials for other indications of rivaroxaban and apixaban are currently underway. The long-term safety and adverse event profiles are as yet unclear. If and when these new medications are approved, they should be used judiciously while issues related to reversibility, long-term adverse events, and monitoring are still unresolved. For some patients, warfarin may continue to be the most appropriate oral anticoagulant medication. JFP

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TABLE W1

Important warfarin interactions*

	Anti-infectives	Cardiovascular drugs	Analgesics	Agents that affect the central nervous system	Agents that affect the GI tract	Herbal supplements	Other
Potentiation	Ciprofloxacin Clarithromycin Cotrimoxazole Erythromycin Fluconazole Gatifloxacin Itraconazole Levofloxacin Metronidazole Tetracycline Voriconazole	Amiodarone Atorvastatin Fenofibrate Fluvastatin Gemfibrozil Lovastatin Propafenone Ropinirole Simvastatin	Acetaminophen Celecoxib Interferon Piroxicam Propoxyphene Tramadol	Alcohol (binge) Citalopram Entacapone Phenytoin Sertraline	Cimetidine Fish oil Mango Omeprazole	Boldo-fenugreek Danshen Dong quai Lycium barbarum L Quilinggao	Anabolic steroids Fluorouracil Gemcitabine Levamisole/fluorouracil Levothyroxine Tamoxifen Tolterodine Zileuton
Inhibition	Dicloxacillin Griseofulvin Nafcillin Rifampin	Bosentan Cholestyramine	Azathioprine Mesalamine	Alcohol Barbiturates Carbamazepine	Avocado (large amounts) Foods and enteral nutrition high in vitamin K Soy milk Sucralfate	Ginseng Green tea	Chelation therapy Mercaptopurine Methimazole Multivitamins Propylthiouracil Raloxifene
Increase bleeding risk		Anticoagulants Antiplatelets	NSAIDs		Alcohol	Garlic Ginkgo Ginseng	

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Not a complete list.

Adapted from: Ansell J, et al. *Chest*. 2008.[4]