Deep Venous Thrombosis and Pulmonary Embolism: Current Therapy

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Pulmonary embolism and deep venous thrombosis are the two most important manifestations of venous thromboembolism (VTE), which is the third most common life-threatening cardiovascular disease in the United States. Anticoagulation is the mainstay of VTE treatment. Most patients with deep venous thrombosis or low-risk pulmonary embolism can be treated in the outpatient setting with low-molecular-weight heparin and a vitamin K antagonist (warfarin) or direct-acting oral anticoagulants. Inpatient treatment of VTE begins with parenteral agents, preferably low-molecular-weight heparin. Unfractionated heparin is used if a patient is hemodynamically unstable or has severe renal insufficiency, high bleeding risk, hemodynamic instability, or morbid obesity. Direct-acting oral anticoagulants are an alternative; however, concerns include cost and use of reversing agents (currently available only for dabigatran, although others are in development). If warfarin, dabigatran, or edoxaban is used, low-molecular-weight or unfractionated heparin must be administered concomitantly for at least five days and, in the case of warfarin, until the international normalized ratio becomes therapeutic for 24 hours. Hemodynamically unstable patients with a low bleeding risk may benefit from thrombolytic therapy. An inferior vena cava filter is not indicated for patients treated with anticoagulation. Current guidelines recommend anticoagulation for a minimum of three months. Special situations, such as active cancer and pregnancy, require long-term use of low-molecular-weight or unfractionated heparin. Anticoagulation beyond three months should be individualized based on a risk/benefit analysis. Symptomatic distal deep venous thrombosis should be treated with anticoagulation, but asymptomatic patients may be monitored with serial imaging for two weeks and treated only if there is extension. (*Am Fam Physician*. 2017;95(5):295-302.

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Deep venous thrombosis (DVT) and pulmonary embolism (PE) are the two most important manifestations of venous thromboembolism (VTE), which is the third most common life-threatening cardiovascular disease, after myocardial infarction and stroke, in the United States.[1] According to the Centers for Disease Control and Prevention, the annual incidence of VTE is one or two per 1,000 persons, and the overall mortality rate is between 60,000 and 100,000 annually.[2] One-half of patients with DVT will have long-term complications, including postthrombotic syndrome and venous ulcers. One-third of patients with VTE will have a recurrence within 10 years.[2]

Approximately one-third of patients with VTE present with PE, and two-thirds present with DVT.[1] Compared with DVT, PE is more often fatal, has a higher recurrence rate, and is associated with more serious long-term complications. Of patients with proximal DVT, 40% have an associated PE, whereas 70% of patients with PE also have DVT.[3]

Similarities in pathogenesis between DVT and PE parallel the similarities in their management, including anticoagulation, risk factor assessment, and perioperative management. For decades, DVT and PE have been treated with unfractionated or low-molecular-weight heparin and the vitamin K antagonist warfarin (Coumadin). Direct-acting oral anticoagulants are a safe and effective alternative to warfarin that are supported by published guidelines.[4,5]

This article includes guidelines for the management of VTE from the American College of Chest Physicians (ACCP), American Academy of Family Physicians, and American College of Physicians.[6-8]

Initial Management

Prompt diagnosis and treatment of VTE with appropriate medications may prevent thrombus extension and embolization, relieve acute symptoms, prevent cardiopulmonary collapse, and reduce the risk of long-term complications. Empiric treatment during the evaluation period is controversial

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Direct-acting oral anticoagulants are an alternative to vitamin K antagonist therapy (warfarin [Coumadin]) for VTE.	A	4, 19, 20
Most patients with deep venous thrombosis and selected patients with pulmonary embolism can be safely treated as outpatients.	B	8, 10, 11
Inferior vena cava filters should be avoided in patients with VTE treated with anticoagulation.	B	8, 9, 26, 27
If there are no contraindications, patients diagnosed with acute VTE should receive anticoagulation for a minimum of three months.	C	8, 9, 29

VTE = venous thromboembolism.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

and not evidence-based. In a hemodynamically unstable patient with a high probability of VTE, intravenous thrombolytic therapy can be considered.[9] Similarly, if there is a delay in obtaining a definitive diagnostic test in a hemodynamically unstable patient with a high probability of VTE, parenteral anticoagulation should be considered until a diagnosis is confirmed.

After diagnosis, most patients with DVT can be treated as an outpatient, except in cases of limb ischemia, significant comorbidities (e.g., end-stage renal disease), functional limitations, high bleeding risk, or nonadherence concerns. Anticoagulation is not recommended for isolated distal DVTs (i.e., confined to calf veins) unless the patient is symptomatic, has risk factors for extension (e.g., unprovoked DVT, prior VTE), or develops extension of DVT on serial imaging for two weeks.[8,10,11]

Evidence supports outpatient treatment of PE if the risk of nonadherence is low and the patient is clinically stable; has no contraindications to anticoagulation, such as recent bleeding, severe renal or liver disease, or platelet count of less than 70×10^3 per mm^3 (70×10^9 per L); and feels capable of managing the disease at home.[8,10] Patients with PE who are hemodynamically unstable (e.g., those with hypotension or evidence of shock) should be admitted to an intensive care unit, and systemic thrombolytic therapy may be considered.[9]

Anticoagulation Choices

Once VTE is diagnosed and the patient is stabilized if needed, anticoagulation should be initiated unless contraindicated. Guideline recommendations for anticoagulation are divided into phases: initial phase (first week after diagnosis), long-term phase (second week to three months), and extended phase (beyond three months).[9]

In the initial phase of anticoagulation, a decision must be made between using the vitamin K antagonist warfarin or a direct-acting oral anticoagulant. If warfarin, dabigatran (Pradaxa), or edoxaban (Savaysa) is selected, concomitant parenteral anticoagulation is required for at least five days. Guidelines recommend low-molecular-weight over unfractionated heparin, which is supported by multiple therapeutic trials showing greater effectiveness and safety and lower mortality.[12] However, unfractionated heparin is preferred in patients with severe renal insufficiency, high bleeding risk, hemodynamic instability, or morbid obesity.[7-9] Apixaban (Eliquis) and rivaroxaban (Xarelto) do not require concomitant use of heparin at initiation. The administration and dosing of anticoagulants are included in *Table 1*.[13]

If a patient is admitted, discharge should occur when the patient has clinically improved and is hemodynamically stable. The initial treatment phase (first week) can be completed in the outpatient setting after thorough patient education on anticoagulation therapy. During the initial three months of anticoagulation, patients should be evaluated periodically for adherence and complications of treatment, especially bleeding. Frequency of physician visits is individualized based on patient knowledge and adherence, and on which therapy is selected.

If warfarin is used, patients require careful education on food and drug interactions and the importance of regular office visits to check international normalized ratio until a steady state is achieved. For selected patients, physician-directed, home-based international normalized ratio monitoring provides a convenient alternative to office visits.[6]

If a direct-acting oral anticoagulant is selected, no routine laboratory monitoring is required, but dose adjustments may be needed for certain agents *(Table 1[13])*. Patients must be educated about adherence and what to do in the event of bleeding.

Direct-Acting Oral Anticoagulants

In 2012, rivaroxaban became the first direct-acting oral anticoagulant approved by the U.S. Food and Drug Administration for treatment of DVT and PE. Several others followed. These agents belong to two classes:

Table 1. Anticoagulants for the Treatment of Pulmonary Embolism and Deep Venous Thrombosis

Drug	*Dosage*	*Half-life*	*Renal dosing*
Direct factor Xa inhibitors			
Apixaban (Eliquis)	10 mg orally twice daily for 7 days, followed by 5 mg orally twice daily	12 hours	27% renal clearance 2.5 mg orally twice daily if at least 1 criterion is met: serum creatinine 1.5 mg per dL (133 µmol per L) or more, age 80 years or older, weight 60 kg (132 lb, 4 oz) or less
Edoxaban (Savaysa)	Adults > 60 kg: 60 mg orally Adults ≤ 60 kg: 30 mg orally once daily following 5 to 10 days of initial therapy with a parenteral anticoagulant	10 to 14 hours	50% renal clearance CrCl 15 to 50 mL per minute per 1.73 m^2 (0.25 to 0.83 mL per second per m^2): 30 mg orally once per day CrCl < 15 mL per minute per 1.73 m^2: avoid use CrCl > 95 mL per minute per 1.73 m^2 (1.59 mL per second per m^2): avoid use
Rivaroxaban (Xarelto)	15 mg orally with food twice daily for 21 days, then 20 mg orally once daily	5 to 9 hours	66% renal clearance CrCl 15 to 80 mL per minute per 1.73 m^2 (0.25 to 1.34 mL per second per m^2): avoid use in patients receiving a combined P-glycoprotein and moderate cytochrome P450 3A4 inhibitor unless the potential benefit justifies the potential risk CrCl ≤ 30 mL per minute per 1.73 m^2 (0.50 per second per m^2): avoid use
Direct thrombin inhibitors			
Dabigatran (Pradaxa)	150 mg orally twice daily following 5 to 10 days of initial therapy with a parenteral anticoagulant	12 to 17 hours	80% renal clearance CrCl ≤ 30 mL per minute per 1.73 m^2: dosing recommendations are not provided by the manufacturer CrCl < 50 mL per minute per 1.73 m^2: avoid use in patients taking a P-glycoprotein inhibitor
Indirect factor Xa inhibitors			
Fondaparinux (Arixtra)	Concomitant treatment with warfarin should be initiated as soon as possible Adults < 50 kg (110 lb, 4 oz): 5 mg subcutaneously once daily Adults 50 to 100 kg (110 lb, 4 oz to 220 lb, 7 oz): 7.5 mg subcutaneously once daily Adults > 100 kg: 10 mg subcutaneously once daily	17 to 21 hours	100% renal clearance CrCl 30 to 50 per minute per 1.73 m^2: use with caution, and consider reducing dosage by 50% CrCl < 30 per minute per 1.73 m^2: avoid use
Low-molecular-weight heparin			
Dalteparin (Fragmin)	100 units per kg subcutaneously every 12 hours, or 200 units per kg subcutaneously once daily	3 to 5 hours	Primarily renally eliminated CrCl < 30 per minute per 1.73 m^2: monitor anti-Xa levels
Enoxaparin (Lovenox)	1 mg per kg subcutaneously every 12 hours, or 1.5 mg per kg subcutaneously every 24 hours	4.5 to 7 hours	Primarily eliminated renally CrCl < 30 per minute per 1.73 m^2: reduce dosage to 1 mg per kg once daily

continues

CrCl = creatinine clearance; INR = international normalized ratio.

direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban).[14-17]

There are logistic benefits of direct-acting anticoagulants compared with warfarin—primarily that no regular monitoring is required because of their predictable pharmacokinetics. Other benefits compared with warfarin include fewer dietary restrictions, fewer drug interactions, and relatively fixed dosing. Rivaroxaban should be taken with food, and it interacts with cytochrome P450 3A4 and P-glycoprotein inhibitors. Dabigatran may be

Table 1. Anticoagulants for the Treatment of Pulmonary Embolism and Deep Venous Thrombosis
(continued)

Drug	*Dosage*	*Half-life*	*Renal dosing*
Fibrinolytics			
Alteplase (Activase)	100-mg intravenous infusion over 2 hours	30 to 45 minutes	Approximately 80% renal clearance No dosage adjustments are needed
Unfractionated heparin	80 units per kg intravenous bolus, then maintenance infusion of 18 units per kg per hour of intravenous continuous infusion; further adjustment per nomogram *or* 8,000 to 10,000 units subcutaneously every 8 hours, or 15,000 to 20,000 units subcutaneously every 12 hours	1 to 5 hours	Primarily cleared and metabolized by the reticuloendothelial system Adjust dosage based on activated partial thromboplastin time
Vitamin K antagonists			
Warfarin (Coumadin)	Initially 5 mg orally or intravenously once daily; consider lower dose in geriatric, malnourished, debilitated patients or patients with congestive heart failure, liver failure, or high bleeding risk Clinical practice guidelines recommend 10 mg orally once daily for the first 2 days for patients healthy enough to be treated as outpatients Warfarin should be started on the same day as heparin, low-molecular-weight heparin, or fondaparinux and continued for ≥ 5 days and until the INR is ≥ 2 for at least 24 hours	21 to 89 hours	Up to 92% of the orally administered dose is recovered in the urine, primarily as metabolites No adjustment, continue to dose based on INR

CrCl = creatinine clearance; INR = international normalized ratio.

Information from reference 13.

affected by P-glycoprotein inducers or inhibitors. Dose adjustment may be required for these medications.[4]

The drawbacks of direct-acting anticoagulants are cost ($349 to $430 per month, U.S. average wholesale price[18]) and uncertainties regarding management of major bleeding or emergent surgery. Direct-acting anticoagulants have shorter half-lives than warfarin, and missed doses or premature discontinuation increases the risk of thrombotic events. Also, because elimination of direct-acting anticoagulants is more dependent on renal function than with warfarin, dose adjustment may be required for patients with chronic kidney disease.[19,20] The initial studies of direct-acting anticoagulants excluded several important patient populations, such as pregnant women, patients with an active cancer diagnosis, and patients who are morbidly obese; thus, there are no data to guide therapy in these groups.[19,20]

Only dabigatran has a commercially available reversal agent, although other reversal agents are in development. In 2015, the U.S. Food and Drug Administration approved idarucizumab (Praxbind), a monoclonal antibody that binds dabigatran in the serum.[21] In instances of major bleeding, there are case series and expert recommendations to guide interventions. For patients experiencing a devastating bleed, such as intracranial hemorrhage, treatment includes stopping the direct-acting anticoagulant; initiating supportive therapy; and administering activated charcoal, antifibrinolytic agents, and prothrombin complex concentrate.[22] Hemodialysis should be considered for severe cases in patients taking dabigatran, but it is not effective for patients taking factor Xa inhibitors.

The ACCP recommends the use of direct-acting anticoagulants over warfarin for VTE treatment in patients without cancer (weak recommendation based on moderate quality evidence, per the ACCP grading system).[8] For patients with recurrent VTE who are already taking an oral anticoagulant, low-molecular-weight heparin is recommended over other oral anticoagulants. For patients with recurrent VTE while taking a low-molecular-weight heparin, the dose should be increased by 25% to 33%

(weak recommendations based on moderate to poor quality evidence per the ACCP grading system).[8]

For patients transitioning from one anticoagulant to another, specific recommendations for conversion are available in *eTable A* and from the U.S. Food and Drug Administration's approved drugs section (http://www.accessdata.fda.gov/scripts/cder/daf/).

Thrombolysis

Because of the high risk of bleeding, thrombolysis is restricted to specific circumstances. Expert consensus guidelines support thrombolytic therapy in patients with persistent hypotension or shock secondary to acute PE.[9] Also, when patients with acute PE who are on anticoagulation deteriorate but are not yet hypotensive, systemic thrombolysis is recommended as long as the risk of bleeding is low.[8] There is better evidence for systemic thrombolysis than for catheter-directed thrombolysis.[8] If systemic thrombolysis fails, catheter-directed thrombolysis is available as a rescue therapy in centers with appropriate expertise. Thrombolysis is not indicated in hemodynamically stable patients with intermediate-risk PE.[23]

Massive proximal lower extremity thrombosis or iliofemoral thrombosis associated with severe symptoms or limb-threatening ischemia for less than 14 days is the only widely accepted indication for thrombolytic therapy in patients with DVT.[9] Treatment modalities include systemic thrombolysis, catheter-directed thrombolysis, and surgical thrombectomy. The most appropriate therapy depends on the treatment center's expertise.

Inferior Vena Cava Filters

An inferior vena cava filter is rarely indicated, and evidence for safety and effectiveness is lacking.[24] If there is an absolute contraindication to therapeutic anticoagulation, complications from anticoagulation, or failure of anticoagulation in a patient with acute proximal DVT, an inferior vena cava filter may be indicated. Its use for other reasons is controversial.[25] Routine use of inferior vena cava filters in patients on anticoagulation does not reduce mortality, even in high-risk patients,[26] and current guidelines recommend against their use in these patients.[8,9] Possible complications from inferior vena cava filter placement include thrombosis and arteriovenous fistula. Retrieval is difficult and has a failure rate of at least 8%.[27]

Treatment Duration

The risk of VTE recurrence is greatest in the first year after the event and remains elevated indefinitely compared with the general population. Lifetime recurrence rates for DVT ranges from 21% to 30%, depending on the population.[10,28] Risk of VTE is increased by patient factors, such as active cancer and thrombophilia.

Long-term anticoagulation reduces the risk of recurrent VTE but results in more bleeding events. Considering this trade-off, it is critical that the duration of anticoagulation therapy be individualized based on the patient's risk of recurrence vs. risk of bleeding. Risk factors for bleeding are summarized in *Table 2*.[9] If there are no contraindications, current guidelines recommend anticoagulation for a minimum of three months for PE and proximal DVT.[8,29] If a reversible provoking factor is identified as the cause of VTE, anticoagulation beyond three months is not recommended.[7-9] Extended anticoagulation is recommended for patients with an unprovoked VTE and low risk of bleeding.[8,9] Indefinite anticoagulation is recommended for patients with a second VTE and low or moderate risk of bleeding.[8,9]

The D-dimer test has been used to stratify risk of recurrent VTE. The D-dimer value is checked one month after anticoagulation ends, with an increased level indicating

Table 2. Risk Factors for Major Bleeding While Taking Anticoagulants

Risk factors

Age > 65 years	Comorbidity and reduced functional capacity	Poor anticoagulant control
Age > 75 years*	Diabetes mellitus	Previous bleeding problems
Alcohol abuse	Frequent falls	Previous stroke
Anemia	Liver failure	Recent surgery
Antiplatelet therapy	Metastatic cancer	Renal failure
Cancer		Thrombocytopenia

	Estimated absolute risk (%)		
Categorization of risk	*Low risk (0 risk factors)*	*Moderate risk (1 risk factor)*	*High risk (≥ 2 risk factors)*
Initial risk (0 to 3 months)	1.6	3.2	12.8
Risk beyond 3 months	0.8	1.6	≥ 6.5

**—Increasing age is an additive risk; therefore, patients older than 75 years are considered to have two risk factors.*

Adapted with permission from Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published correction appears in Chest. *2012;142(6):1698-1704].* Chest. *2012;141 (2 suppl):e432s.*

Table 3. Special Considerations in the Treatment of VTE

Consideration	*Recommendations*
Aspirin for extended treatment of VTE	Aspirin is generally not considered a reasonable alternative to anticoagulant therapy. If a patient has decided to stop anticoagulants, aspirin can be considered for prevention of recurrent VTE. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.[8]
Chronic thromboembolic pulmonary hypertension	An evaluation for possible thromboendarterectomy by an experienced team should be considered.[8] In patients with inoperable chronic thromboembolic pulmonary hypertension or persistent pulmonary hypertension after thromboendarterectomy, referral to a team with expertise in the evaluation and management of pulmonary hypertension is generally warranted.
Distal DVT	If the patient is symptomatic, treat with anticoagulation. If the patient does not have severe symptoms or risk factors for extension, perform serial imaging of the deep veins for 2 weeks over initial anticoagulation. No anticoagulation is needed if no extension of thrombus is detected. Anticoagulation should be initiated if DVT extends into the proximal veins.[6]
Perioperative management	In patients with acute VTE, surgery should be delayed until 3 months of treatment have elapsed, if possible. If emergent surgery is needed, anticoagulation reversal and/or bridging may be needed.[31] For patients on extended VTE treatment to prevent recurrence (after the first 3 months), an individualized decision about perioperative anticoagulation must be reached based on a risk/benefit analysis.
Postthrombotic syndrome	Ambulation should be encouraged.[9] Evidence does not support the use of compression stockings for prevention of postthrombotic syndrome.[32] Catheter-directed thrombolysis increases the patency of veins and reduces the incidence of postthrombotic syndrome by one-third.[33]
Subsegmental pulmonary embolism	Isolated subsegmental pulmonary embolism may be overdiagnosed because of breathing motion and beam-hardening artifacts.[34] There is limited evidence to determine the effectiveness and safety of anticoagulation therapy in patients with subsegmental pulmonary embolism.[35] The 2016 American College of Chest Physicians guideline states that anticoagulation should not be used in patients with subsegmental pulmonary embolism if they do not have proximal DVT and are at low risk of recurrence.[8]
Superficial venous thrombosis	Patients with superficial venous thrombosis are at higher risk of developing DVT. Consider anticoagulation in extensive cases and in those associated with involvement above the knee, particularly if close to the saphenofemoral junction or the greater saphenous vein; severe symptoms; history of VTE or superficial venous thrombosis; active cancer; or recent surgery.[9,36] If the decision is made to anticoagulate, treat with LMWH or fondaparinux (Arixtra) for 4 to 6 weeks.[37]
Upper extremity DVT	This is most often associated with a central venous catheter and is treated similarly to lower extremity DVT.
VTE in morbidly obese patient	Morbidly obese patients are usually excluded from clinical trials of anticoagulants. Data are lacking regarding direct-acting oral anticoagulants. Heparin can be used in the initial treatment of VTE. The LMWH dose should be based on total body weight for the treatment of VTE. Refer to the manufacturer's directions for individual medications because some may recommend a maximum dose despite patient weight.[38]
VTE in patients with active cancer	LMWH is preferred over warfarin or direct-acting oral anticoagulants for VTE treatment.[8] Consider extended anticoagulation if the bleeding risk is low.[9]
VTE in pregnancy	LMWH is the preferred agent.[39] Warfarin (Coumadin) is teratogenic; avoid in pregnancy. Direct-acting oral anticoagulants are not tested in pregnant patients; therefore, their safety is unknown; avoid in pregnancy. Anticoagulation should be continued for at least 3 months and at least 6 weeks postpartum.

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism.

Information from references 6, 8, 9, and 31 through 39.

BEST PRACTICES IN HEMATOLOGY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	*Sponsoring organization*
Do not recommend bed rest following diagnosis of acute deep venous thromboembolism after the initiation of anticoagulation therapy, unless significant medical concerns are present.	American Physical Therapy Association
Do not treat with an anticoagulant for more than three months in a patient with a first venous thromboembolism occurring in the setting of a major transient risk factor.	American Society of Hematology

Source: For more information on the Choosing Wisely Campaign, see http://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see http://www.aafp.org/afp/recommendations/search.htm.

increased risk.[30] However, the ACCP does not recommend its routine use to determine appropriate candidates for indefinite anticoagulation.[8]

Special Considerations

Some conditions, such as pregnancy and cancer, require special consideration when treating VTE. These special considerations are described in *Table 3*.[6,8,9,31-39] The ACCP does not recommend routine use of compression stockings to prevent postthrombotic syndrome. For patients with low-risk subsegmental PE without proximal DVT, clinical surveillance is preferred over anticoagulation.[8]

This article updates a previous article on this topic by Ramzi and Leeper.[40]

Data Sources: We searched PubMed, Cochrane database, Essential Evidence, and guidelines.gov using the following terms in various combinations: management, treatment, therapy, venous thromboembolism, deep venous thrombosis, pulmonary embolus, antithrombotic therapy, direct-acting oral anticoagulants, and new oral anticoagulants. Search dates: September 2015 to February 2016, and December 10, 2016.

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REFERENCES

1. Nielsen JD. The incidence of pulmonary embolism during deep vein thrombosis. *Phlebology*. 2013;28(suppl 1):29-33.
2. Centers for Disease Control and Prevention. Venous thromboembolism (blood clots). Data and statistics. June 22, 2015. http://www.cdc.gov/ncbddd/dvt/data.html. Accessed November 29, 2015.
3. Wilbur J, Shian B. Diagnosis of deep venous thrombosis and pulmonary embolism. *Am Fam Physician*. 2012;86(10):913-919.
4. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism [published correction appears in *JAMA*. 2014;311(24):2545]. *JAMA*. 2014;311(7):717-728.
5. Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. *Am Fam Physician*. 2013;87(8):556-566.
6. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e44S-88S.
7. Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians [published correction appears in *Ann Fam Med*. 2007;5(2):179]. *Ann Fam Med*. 2007;5(1):74-80.
8. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
9. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published correction appears in *Chest*. 2012;142(6):1698-1704]. *Chest*. 2012;141(2 suppl):e419S-494S.
10. Yeager BF, Matheny SC. Low-molecular-weight heparin in outpatient treatment of DVT. *Am Fam Physician*. 1999;59(4):945-952.
11. Aujesky D, Roy PM, Verschuren F. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011;378(9785):41-48.
12. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev*. 2010;(9):CD001100.
13. Physicians' Desk Reference. http://www.pdr.net. Accessed January 18, 2016.
14. PDR.net. Pradaxa (dabigatran etexilate mesylate)—drug summary. 2016. http://www.pdr.net/drug-summary/Pradaxa-dabigatran-etexilate-mesylate-100. Accessed December 16, 2016.
15. PDR.net Xarelto (rivaroxaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Xarelto-rivaroxaban-278. December 16, 2016.
16. PDR.net. Eliquis (apixaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Eliquis-apixaban-3039. December 16, 2016.
17. PDR.net. Savaysa (edoxaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Savaysa-edoxaban-3667. December 16, 2016.
18. Lexicomp online. http://online.lexi.com [login required]. Accessed July 1, 2016.
19. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. *Cochrane Database Syst Rev*. 2015;(12):CD010957.
20. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. *Cochrane Database Syst Rev*. 2015;(6):CD010956.
21. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-520.
22. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors [published correction appears in *Am J Hematol*. 2012;87(7):748]. *Am J Hematol*. 2012;87(suppl 1):S141-S145.
23. Meyer G, Vicaut E, Danays T, et al.; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402-1411.

24. Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. *Cochrane Database Syst Rev.* 2010;(2):CD006212.
25. Sing RF, Fischer PE. Inferior vena cava filters: indications and management. *Curr Opin Cardiol.* 2013;28(6):625-631.
26. Mismetti P, Laporte S, Pellerin O, et al.; PREPIC2 Study Group. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627-1635.
27. Lee MJ, Valenti D, de Gregorio MA, Minocha J, Rimon U, Pellerin O. The CIRSE retrievable IVC filter registry: retrieval success rates in practice. *Cardiovasc Intervent Radiol*. 2015;38(6):1502-1507.
28. Hansson PO, Sörbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med*. 2000;160(6):769-774.
29. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. *Blood*. 2014;123(12):1794-1801.
30. Palareti G, Cosmi B, Legnani C, et al.; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy [published correction appears in *N Engl J Med*. 2006;355(26):2797]. *N Engl J Med*. 2006;355(17):1780-1789.
31. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published correction appears in *Chest*. 2012;141(4):1129]. *Chest*. 2012;141(2 suppl):e326S-350S.
32. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome. *Lancet*. 2014;383(9920):880-888.
33. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev.* 2014;(1):CD002783.
34. Hutchinson BD, Navin P, Marom EM, Truong MT, Bruzzi JF. Overdiagnosis of pulmonary embolism by pulmonary CT angiography. *AJR Am J Roentgenol*. 2015;205(2):271-277.
35. Yoo HH, Queluz TH, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database Syst Rev.* 2014;(4):CD010222.
36. Leizorovicz A, Becker F, Buchmüller A, Quéré I, Prandoni P, Decousus H; CALISTO Study Group. Clinical relevance of symptomatic superficial-vein thrombosis extension: lessons from the CALISTO study. *Blood*. 2013;122(10):1724-1729.
37. Scott G, Mahdi AJ, Alikhan R. Superficial vein thrombosis: a current approach to management. *Br J Haematol*. 2015;168(5):639-645.
38. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43(6):1064-1083.
39. Bates SM. Pregnancy-associated venous thromboembolism: prevention and treatment. *Semin Hematol*. 2011;48(4):271-284.
40. Ramzi DW, Leeper KV. DVT and pulmonary embolism: part II. Treatment and prevention. *Am Fam Physician*. 2004;69(12):2841-2848.

eTable A. Conversions for Direct-Acting Oral Anticoagulants for Venous Thromboembolism Therapy

	Conversions	
Direct-acting anticoagulant	*Switching to or from the vitamin K antagonist warfarin (Coumadin)*	*Switching to or from nonwarfarin anticoagulants*
Apixaban (Eliquis): 10 mg twice per day for 7 days, then 5 mg twice per day	From warfarin to apixaban: Discontinue warfarin and initiate apixaban when INR is < 2.0. To warfarin from apixaban: Discontinue apixaban and begin both a parenteral anticoagulant and warfarin when the next dose of apixaban is due; discontinue parenteral anticoagulant when INR reaches the target range.	From oral or parenteral anticoagulants to apixaban: Discontinue anticoagulant and begin apixaban when the next dose of the anticoagulant is due. To oral or parenteral anticoagulants from apixaban: Discontinue apixaban and begin the new anticoagulant when the next dose of apixaban is due.
Dabigatran (Pradaxa): 150 mg twice per day after 5 to 10 days of parenteral anticoagulation	From warfarin to dabigatran: Discontinue warfarin and initiate dabigatran when INR is < 2.0. To warfarin from dabigatran based on CrCl: CrCl ≥ 50 mL per minute per 1.73 m^2 (0.83 mL per second per m^2): initiate warfarin 3 days before discontinuation of dabigatran. CrCl 30 to 50 mL per minute per 1.73 m^2 (0.50 to 0.83 mL per second per m^2): initiate warfarin 2 days before discontinuation of dabigatran. CrCl 15 to 30 mL per minute per 1.73 m^2 (0.25 to 0.50 mL per second per m^2): initiate warfarin 1 day before discontinuation of dabigatran. CrCl < 15 mL per minute per 1.73 m^2: not recommended.	From a parenteral anticoagulant to dabigatran: Initiate dabigatran ≤ 2 hours before the next dose of the parenteral anticoagulant is due or at the time of discontinuation for a continuously administered parenteral drug; discontinue parenteral anticoagulant at the time of dabigatran initiation. To a parenteral anticoagulant from dabigatran: Wait 12 hours (CrCl ≥ 30 mL per minute per 1.73 m^2) or 24 hours (CrCl < 30 mL per minute per 1.73 m^2) after the last dose of dabigatran before initiating a parenteral anticoagulant.
Edoxaban (Savaysa): 60 mg every 24 hours after 5 to 10 days of initial therapy with a parenteral anticoagulant	From warfarin to edoxaban: Discontinue warfarin and start edoxaban when the INR is < 2.5. To warfarin from edoxaban: For patients taking 60 mg, reduce dose to 30 mg and begin warfarin concomitantly. For patients taking 30 mg, reduce dose to 15 mg and begin warfarin concomitantly. INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Discontinue edoxaban and continue warfarin once a stable INR of > 2 is achieved. Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and warfarin when the next dose of edoxaban is due; once a stable INR of > 2.0 is achieved, discontinue parenteral anticoagulant and continue warfarin.	From continuous infusion of unfractionated heparin to edoxaban: Discontinue heparin infusion and initiate edoxaban 4 hours later. From LMWH to edoxaban: Discontinue LMWH and initiate edoxaban when the next dose of LMWH is due. From oral anticoagulants to edoxaban: Discontinue current oral anticoagulant and initiate edoxaban when the next dose of the initial oral anticoagulant is due. To a parenteral anticoagulant or oral anticoagulant from edoxaban: Discontinue edoxaban and start the other oral anticoagulant when the next dose of edoxaban is due.

continues

CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin.

eTable A. Conversions for Direct-Acting Oral Anticoagulants for Venous Thromboembolism Therapy
(continued)

	Conversions	
Direct-acting anticoagulant	*Switching to or from the vitamin K antagonist warfarin (Coumadin)*	*Switching to or from nonwarfarin anticoagulants*
Rivaroxaban (Xarelto): 15 mg twice per day for 21 days, 20 mg once per day (should be taken with food)	From warfarin to rivaroxaban: Discontinue warfarin and initiate rivaroxaban as soon as the INR decreases to < 3.0. To warfarin from rivaroxaban: Discontinue rivaroxaban and initiate warfarin and a parenteral anticoagulant when the next dose of rivaroxaban is due.	From continuous infusion of unfractionated heparin to rivaroxaban: Initiate rivaroxaban at the time of heparin discontinuation. From anticoagulants (other than continuous infusion of unfractionated heparin) to rivaroxaban: Discontinue current anticoagulant and initiate rivaroxaban ≤ 2 hours before the next evening dose of the discontinued anticoagulant is due. To other anticoagulants (other than warfarin) from rivaroxaban: Discontinue rivaroxaban and initiate the anticoagulant when the next dose of rivaroxaban is due.

CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin.

Information from:

PDR.net. Eliquis (apixaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Eliquis-apixaban-3039. Accessed January 18, 2016.

PDR.net. Pradaxa (dabigatran etexilate mesylate)—drug summary. 2016. http://www.pdr.net/drug-summary/Pradaxa-dabigatran-etexilate-mesylate-100. Accessed January 18, 2016.

PDR.net. Savaysa (edoxaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Savaysa-edoxaban-3667. Accessed January 18, 2016.

PDR.net. Xarelto (rivaroxaban)—drug summary. 2016. http://www.pdr.net/drug-summary/Xarelto-rivaroxaban-278. Accessed January 18, 2016.