Anticoagulation therapy is recommended for preventing, treating, and reducing the recurrence of venous thromboembolism, and preventing stroke in persons with atrial fibrillation. Direct oral anticoagulants are first-line agents for eligible patients for treating venous thromboembolism and preventing stroke in those with nonvalvular atrial fibrillation. Vitamin K antagonists are recommended for patients with mechanical valves and valvular atrial fibrillation. Vitamin K antagonists inhibit the production of vitamin K–related factors and require a minimum of five days overlap with parenteral anticoagulants, whereas direct oral anticoagulants directly inhibit factor II or factor Xa, providing more immediate anticoagulation. The immediate effect of direct oral anticoagulants permits select patients at low risk to initiate treatment in the outpatient setting for venous thromboembolism, including pulmonary embolism. Low-molecular-weight heparin continues to be recommended as a first-line treatment for patients with venous thromboembolism and active cancer, although there is growing evidence of effectiveness for the use of direct oral anticoagulants in this patient population. Validated bleeding risk assessments such as HAS-BLED should be performed at each visit and modifiable factors should be addressed. Major bleeding should be treated with vitamin K and 4-factor prothrombin complex concentrate for patients already being treated with a vitamin K antagonist. Idarucizumab has been effective for reversing the anticoagulant effects of dabigatran, and andexanet alfa has been effective for reversing the effects of rivaroxaban and apixaban. (Am Fam Physician. 2019;100(7):426-434. Copyright © 2019 American Academy of Family Physicians.)


**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 398.

**Author disclosure:** No relevant financial affiliations.
is in the targeted therapeutic range for a minimum of 24 hours. The targeted INR range depends on indication for use and, at times, patient comorbidities.

For most patients, vitamin K antagonists should be initiated at a maintenance dosage of 5 mg per day. Older patients and persons with liver disease, poor nutritional status, or heart failure may require lower initiation dosages. Diarrhea, fever, and hyperthyroidism can also potentiate the effect of vitamin K antagonists. Genetic factors can predispose patients to reduced vitamin K antagonist requirements,

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Suggest initiating aspirin to prevent future VTE in patients with an unprovoked DVT or PE who decide to stop anticoagulation (grade 2B)</td>
<td>Aspirin should not be considered a substitute for anticoagulation but is suggested for patients who wish to stop therapy and not pursue lifelong anticoagulation following an unprovoked DVT or PE</td>
</tr>
<tr>
<td>Direct oral anticoagulants</td>
<td>Recommended for outpatient treatment of non–cancer-associated provoked or unprovoked VTE over vitamin K antagonists (grade 2B) and LMWH (grade 2C)</td>
<td>Simplification of anticoagulation management: no need for frequent dosage adjustments or international normalized ratio monitoring</td>
</tr>
<tr>
<td>LMWH</td>
<td>Recommended for outpatient treatment of cancer-associated provoked or unprovoked VTE over direct oral anticoagulants (grade 2C) and vitamin K antagonists (grade 2B)</td>
<td>Two studies have demonstrated a reduction in recurrence of VTE in patients with cancer treated with a direct oral anticoagulant (e.g., rivaroxaban, edoxaban [Savaysa]) compared with LMWH (e.g., dalteparin [Fragmin]); however, the studies also demonstrated an increased risk of bleeding, specifically in patients with esophageal or gastroesophageal cancer^15 CHEST guidelines have not been updated in response to these studies*</td>
</tr>
<tr>
<td>Location of care</td>
<td>Suggest care at home or early discharge for patients with low-risk PE who have adequate home support (grade 2B)</td>
<td>Criteria: clinically stable; no recent bleeding, no advanced renal disease, no advanced hepatic disease, no thrombocytopenia (&lt; 70 × 10^9 per L); adequate support at home and ability to adhere to regimen; patient feels comfortable with home care; no evidence of right ventricular dysfunction; normal cardiac biomarkers Pulmonary Embolism Severity Index may be used to help stratify risk</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>Suggest changing to LMWH if recurrence while on vitamin K antagonists or direct oral anticoagulants (grade 2C) If recurrence while on LMWH, suggest increasing dose by one-fourth to one-third (grade 2C)</td>
<td>If unable to increase intensity, consider insertion of an inferior vena cava filter</td>
</tr>
<tr>
<td>Subsegmental PE</td>
<td>Low-risk subsegmental PE without proximal DVT, suggest surveillance instead of anticoagulation (grade 2C), suggest anticoagulation if higher risk of recurrence (grade 2C)</td>
<td>Factors associated with true subsegmental PE compared with a false-positive result on computed tomography: high-quality imaging; multiple filling defects; defects in proximal subsegmental vessels; multiple images with same defect; defect surrounded by contrast; symptoms consistent with PE; multiple views with defect; high pretest probability for PE; positive unexplained D-dimer assay results</td>
</tr>
</tbody>
</table>

Note: Grade 1 recommendations are strong recommendations that can be applied to most patients; grade 2 recommendations are weaker recommendations. Grade A recommendations are supported by high-quality evidence, grade B recommendations are based on randomized clinical trials with methodologic flaws or inconsistent results; and grade C recommendations are based on weaker evidence.

*—The 2019 National Comprehensive Cancer Network guidelines on cancer-associated VTE includes rivaroxaban (Xarelto) and edoxaban (Savaysa) as first-line options. Edoxaban should be initiated with LMWH or unfractionated heparin for five days.

Andexanet alfa (Andexxa) is available to reverse apixaban (Eliquis) and rivaroxaban (Xarelto), and idarucizumab (Praxbind) is available to reverse dabigatran (Pradaxa) | Andexanet alfa (Andexxa) is available to reverse apixaban (Eliquis) and rivaroxaban (Xarelto), and idarucizumab (Praxbind) is available to reverse dabigatran (Pradaxa) |

Subsegmental PE | Low-risk subsegmental PE without proximal DVT, suggest surveillance instead of anticoagulation (grade 2C), suggest anticoagulation if higher risk of recurrence (grade 2C) | Factors associated with true subsegmental PE compared with a false-positive result on computed tomography: high-quality imaging; multiple filling defects; defects in proximal subsegmental vessels; multiple images with same defect; defect surrounded by contrast; symptoms consistent with PE; multiple views with defect; high pretest probability for PE; positive unexplained D-dimer assay results |

| Location of care | Suggest care at home or early discharge for patients with low-risk PE who have adequate home support (grade 2B) | Criteria: clinically stable; no recent bleeding, no advanced renal disease, no advanced hepatic disease, no thrombocytopenia (< 70 × 10^9 per L); adequate support at home and ability to adhere to regimen; patient feels comfortable with home care; no evidence of right ventricular dysfunction; normal cardiac biomarkers Pulmonary Embolism Severity Index may be used to help stratify risk |

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism. Information from references 1-5.
Although there is a small subset of patients who may have unexpected responses to vitamin K antagonists, it is not currently recommended that patients undergo genetic testing.

After a baseline INR is determined, the next INR should be obtained after the patient has received two or three doses of the vitamin K antagonist. Monitoring should then be decreased to twice weekly until the INR is within the therapeutic range, then decreased to weekly, every other week, and finally monthly. The ACCP guidelines recommend INR monitoring once every 12 weeks for patients who are stable (defined as at least three months of consistent results with no required adjustment of vitamin K antagonist dosing).

If the patient’s INR becomes subtherapeutic or supra-therapeutic, the frequency of monitoring should be increased until the INR stabilizes again. The ACCP guidelines recommend INR monitoring once every 12 weeks for patients who are stable (defined as at least three months of consistent results with no required adjustment of vitamin K antagonist dosing).

### Table 2: American College of Chest Physicians Recommendations for Indication, Agent, and Duration of Anticoagulation Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of DVT of the leg or PE</td>
<td>Direct oral anticoagulants over vitamin K antagonists (grade 2B) and LMWH (grade 2C)</td>
<td>First episode of proximal DVT or PE attributed to reversible risk factor or surgery: Three months recommended over short-term use (grade 1B), longer use (grade 1B), or extended therapy (grade 1B) First episode of unprovoked proximal DVT or PE not attributed to a reversible risk factor: Low or moderate bleeding risk: extended use (lifelong) recommended over three months (grade 2B); high bleeding risk: three months recommended over extended use (grade 1B); recommend reassessing bleeding risk annually First episode of distal DVT attributed to a surgery or reversible risk factor: If without severe symptoms or risk factors of extension, suggest serial ultrasonography surveillance for two weeks instead of anticoagulation (grade 2C); if surveillance shows extension, recommend anticoagulation (grade 2C if it does not extend into proximal vessels; grade 1B if it extends into proximal vessels) If severe symptoms or risk factors of extension, recommend three months treatment over extended use (grade 1B) Risk factors for extension: unexplained d-dimer results; extensive DVT (&gt; 5 cm) and/or involving multiple veins; close to proximal vein; unprovoked; cancer; previous VTE; inpatient</td>
</tr>
<tr>
<td>Cancer*</td>
<td>LMWH over direct oral anticoagulants (grade 2C) and vitamin K antagonists (grade 2B)</td>
<td>Extended therapy (lifelong) recommended (grade 1B if low bleeding risk, grade 2B if high bleeding risk)</td>
</tr>
<tr>
<td>Second episode of DVT of the leg or PE</td>
<td>Suggest changing to LMWH if recurrence while on vitamin K antagonist or direct oral anticoagulant (grade 2C) If recurrence while on LMWH, suggest increasing dose by one-fourth to one-third (grade 2C)</td>
<td>After two episodes of unprovoked DVT or PE, extended therapy if low (grade 1B) or moderate (grade 2B) bleeding risk, three months suggested over extended therapy (lifelong) if high bleeding risk (grade 1B)</td>
</tr>
<tr>
<td>Following completion of anticoagulation therapy, when indicated</td>
<td>Suggest aspirin if unprovoked proximal DVT or PE (grade 2B) and patient elects to discontinue anticoagulation</td>
<td>Extended therapy (lifelong)</td>
</tr>
</tbody>
</table>

**Note:** Grade 1 recommendations are strong recommendations that can be applied to most patients; grade 2 recommendations are weaker recommendations. Grade A recommendations are supported by high-quality evidence, grade B recommendations are based on randomized clinical trials with methodologic flaws or inconsistent results, and grade C recommendations are based on weaker evidence.

*Program stat recommendation: The 2019 National Comprehensive Cancer Network guidelines on cancer-associated VTE includes rivaroxaban and edoxaban as first-line options. Edoxaban should be initiated with LMWH or unfractionated heparin for five days.*

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

Information from reference 1.
provides recommendations for managing supratherapeutic INRs (Table 3).4

Vitamin K antagonists should be taken at the same time every day. An advantage to evening administration is the ability to adjust or hold the dose the same day that the INR result becomes available. If the INR is not within the desired therapeutic range after excluding explanatory factors, a 5% to 20% increase or decrease in the total weekly dosage is recommended.6,7 Patients should be provided with the simplest regimen to achieve the new total weekly dosage.

Drug and Food Interactions. Vitamin K antagonists are subject to many drug interactions. Select drug-drug interactions that are considered to potentiate or inhibit the effects of vitamin K antagonists are listed in Table 4.8 When an interacting drug is initiated or discontinued, more frequent INR checks are recommended. The timing depends on the type of interaction, what the interacting drug is, and the clinical judgement of the physician.

Foods with high vitamin K concentrations, such as leafy green vegetables, have the potential to partially reverse anti-coagulation effects of the vitamin K antagonist.4 A consistent diet is more important than limiting dietary vitamin K.

LOW-MOLECULAR-WEIGHT HEPARIN

Considerations for parenteral medications are provided in eTable A. Dalteparin (Fragmin) and enoxaparin (Lovenox) are commonly used LMWHs in clinical practice. LMWH is derived from unfractionated heparin and has an increased affinity for factor Xa relative to thrombin.4 LMWH’s anti-coagulant effect is primarily from factor Xa inhibition because of its smaller size and its lessened ability to inactivate thrombin compared with unfractionated heparin. Subcutaneous LMWH has a predictable absorption and degree of anticoagulation, so monitoring with anti-factor Xa levels is not routinely recommended. Although LMWH has a similar bleeding risk and lower heparin-induced thrombocytopenia risk compared with unfractionated heparin, a patient with a history of heparin-induced thrombocytopenia should not take LMWH.1

DIRECT ORAL ANTIKAOGULANTS

Warfarin was approved in 1954, and no other oral option existed for patients requiring long-term anticoagulation

<table>
<thead>
<tr>
<th>INR Management</th>
<th>Vitamin K dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than goal INR, but &lt; 4.5</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Option 1: Decrease or hold dosage, increase frequency of monitoring, and resume at lower dosage once INR is within the therapeutic range Option 2: Continue current dosage if INR is minimally elevated (0.5 or less above therapeutic range in a previously stable patient; grade 2C)</td>
<td></td>
</tr>
<tr>
<td>4.5 to 10</td>
<td>No vitamin K (grade 2B)</td>
</tr>
<tr>
<td>Hold next one or two doses, increase frequency of monitoring, and resume at lower dosage once INR is within the therapeutic range</td>
<td>Not applicable</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>2.5 to 5 mg orally as one dose</td>
</tr>
<tr>
<td>Hold vitamin K antagonist and administer vitamin K (grade 2C), increase frequency of monitoring, repeat vitamin K as necessary, and resume vitamin K antagonist at an appropriate dosage when INR is within the therapeutic range</td>
<td></td>
</tr>
</tbody>
</table>

Note: Grade 1 recommendations are strong recommendations that can be applied to most patients; grade 2 recommendations are weaker recommendations. Grade A recommendations are supported by high-quality evidence, grade B recommendations are based on randomized clinical trials with methodologic flaws or inconsistent results, and grade C recommendations are based on weaker evidence.

INR = international normalized ratio.

Information from reference 4.

**TABLE 3**

**Management of Supratherapeutic INRs in Patients Without Significant Bleeding**

**TABLE 4**

**Select Vitamin K Antagonist Drug-Drug Interactions**

**Antimicrobials**
- Ciprofloxacin
- Clarithromycin (Biaxin)
- Erythromycin
- Fluconazole (Diflucan)
- Isoniazid
- Metronidazole (Flagyl)
- Trimethoprim/sulfamethoxazole
- Voriconazole (Vfend)

**Cardiovascular**
- Amiodarone
- Fluvasatin (Lescol)
- Gemfibrozil (Lopid)
- Lovastatin (Mevacor)

**Complementary and alternative medicine**
- Devil’s claw
- Garlic
- Ginkgo biloba

**Miscellaneous**
- Alcohol (acute ingestion)
- Phenytoin (Dilantin)
- Sertraline (Zoloft)

*—Multiple medications increase bleeding risk because of antiplatelet activity (e.g., aspirin, salicylates, nonsteroidal anti-inflammatory drugs).

Information from reference 8.
therapy until 2010 when the direct thrombin inhibitor dabigatran (Pradaxa) was approved. Since dabigatran’s approval, four additional direct oral factor Xa inhibitors have been approved. Characteristics of these anticoagulants are provided in Table 5 and eTable B. Physicians should not automatically consider all patients taking vitamin K antagonists to be good candidates for direct oral anticoagulants because of the diversity in the characteristics of these medications.

Direct oral anticoagulants are first-line agents for eligible patients for the treatment of VTE and prevention of stroke in patients with nonvalvular atrial fibrillation. Compared with vitamin K antagonists, direct oral anticoagulants have the advantage of not requiring direct monitoring, having minimal drug-food interactions, and having a quicker onset of action to therapeutic effect. Direct oral anticoagulants have fewer overall drug-drug interactions (Table 6); a comparable (if not lower) bleeding rate; a shorter half-life; and fixed dosing based on indication, drug interactions, and renal or hepatic function. Among the direct oral anticoagulants, there are key differences including the need for parenteral anticoagulation lead-in, once or twice per day dosing, and degree of renal excretion. Of the direct oral anticoagulants, dabigatran and edoxaban (Savaysa) have the highest renal elimination (approximately 80% and 50%, respectively) and should be used with caution in patients with renal impairment. Each of the direct oral anticoagulants has a risk of bleeding. Compared with vitamin K antagonists and with other direct oral anticoagulants, apixaban (Eliquis) has less major bleeding. In addition, rivaroxaban (Xarelto) and dabigatran have a higher risk of gastrointestinal bleeding compared with apixaban.

Real world experience with direct oral anticoagulants in terms of safety and effectiveness seems consistent with published trials.

### Stroke Prevention in Atrial Fibrillation

In patients who have had acute ischemic stroke, the prevalence of comorbid atrial fibrillation is increasing, and atrial fibrillation–associated strokes have a higher mortality rate. One study found that treatment decisions are often not guideline adherent. The CHADS2 (congestive heart failure; hypertension; age 75 years or older; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism [doubled]) tool (https://www.mdcalc.com/chads2-score-atrial-fibrillation-stroke-risk) or CHA2DS2-VASc (congestive heart failure; hypertension; age 75 years or older [doubled]; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65 to 74 years; sex category) tool (https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk) can

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**TABLE 5**

<table>
<thead>
<tr>
<th>Transition</th>
<th>Apixaban (Eliquis)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Edoxaban (Savaysa)</th>
<th>Rivaroxaban (Xarelto)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From vitamin K antagonists to direct oral anticoagulants</td>
<td>Discontinue vitamin K antagonist; start when INR &lt; 2.0</td>
<td>Discontinue vitamin K antagonist; start when INR &lt; 2.0</td>
<td>Discontinue vitamin K antagonist; start when INR ≤ 2.5</td>
<td>Discontinue vitamin K antagonist; start when INR &lt; 3.0</td>
</tr>
<tr>
<td>From direct oral anticoagulants to LMWH</td>
<td>Discontinue direct oral anticoagulant; start LMWH at time of next scheduled direct oral anticoagulant dose</td>
<td>Discontinue direct oral anticoagulant; start LMWH 12 hours (CrCl ≥ 30 mL per minute per 1.73 m²/[0.50 mL per second per m²]) or 24 hours (CrCl &lt; 30 mL per minute per 1.73 m²) after last direct oral anticoagulant dose</td>
<td>Discontinue direct oral anticoagulant; start LMWH at time of next scheduled direct oral anticoagulant dose</td>
<td>Discontinue direct oral anticoagulant; start LMWH at the time of next scheduled direct oral anticoagulant dose</td>
</tr>
<tr>
<td>From LMWH to direct oral anticoagulants</td>
<td>Discontinue LMWH; start direct oral anticoagulant at time of next scheduled LMWH dose</td>
<td>Discontinue LMWH; start direct oral anticoagulant 0 to 2 hours before time of next LMWH dose</td>
<td>Discontinue LMWH; start direct oral anticoagulant at time of next scheduled LMWH dose</td>
<td>Discontinue LMWH; start direct oral anticoagulant 0 to 2 hours before next scheduled LMWH dose</td>
</tr>
<tr>
<td>From direct oral anticoagulants to vitamin K antagonists</td>
<td>Discontinue direct oral anticoagulant; start parenteral anticoagulant and vitamin K antagonist at time of next direct oral anticoagulant dose</td>
<td>Refer to package insert for specific instructions on direct oral anticoagulant discontinuation and CrCl</td>
<td>Reduce direct oral anticoagulant dose by 50% and start vitamin K antagonist concurrently; discontinue direct oral anticoagulant when stable INR ≥ 2.0</td>
<td>Per manufacturer, no clinical data exist to guide conversion; one approach: discontinue direct oral anticoagulant; start parenteral anticoagulant and vitamin K antagonist at time of next direct oral anticoagulant dose</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NA = not applicable.

Information from references 9-13.
be used to estimate the risk of stroke. American Academy of Family Physicians (AAFP) guidelines recommend the use of oral anticoagulants with a CHADS² score higher than 1. These guidelines also allow for anticoagulation in patients with a CHADS² score of 1 in certain circumstances. The recently published American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend a direct oral anticoagulant over vitamin K antagonists, unless the patient has moderate-to-severe mitral stenosis or a mechanical heart valve. Anticoagulation is recommended for male patients with a CHA²DS²-VASC score of 2 or higher and female patients with a CHA²DS²-VASC score of 3 or higher. AHA/ACC/HRS guidelines attempt to further specify recommendations for low-risk patients as defined by low CHA²DS²-VASC scores.

According to these recommendations, a CHA²DS²-VASC score as low as 1 for men and 2 for women warrants consideration for anticoagulation therapy. Guidelines also recommend that if a therapeutic INR range of 2 to 3 cannot be attained more than 70% of the time, then consideration should be given to changing the treatment to a direct oral anticoagulant. Direct oral anticoagulants or vitamin K antagonists can also be used for the periods before and after cardioversion. Compared with vitamin K antagonists, direct oral anticoagulants are associated with a reduction in the incidence of stroke of 21% to 35% and a reduction in the incidence of intracranial hemorrhage of 33% to 60%.

One comparative effectiveness analysis looked at the treatment of patients with atrial fibrillation who may not have been well-represented in clinical trials because of multiple comorbidities. This study used Medicare data to compare vitamin K antagonists with dabigatran and rivaroxaban in patients with atrial fibrillation and multiple chronic conditions. The study found that effectiveness was similar for all oral anticoagulants and risk of major hemorrhage was reduced among dabigatran users when compared with rivaroxaban (but not vitamin K antagonists) in patients with a

### TABLE 6

<table>
<thead>
<tr>
<th>Direct oral anticoagulant</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Avoid with combined P-glycoprotein inducer† and strong CYP3A4 inducer†</td>
<td>Reduce dose or avoid use with combined P-glycoprotein* and strong CYP3A4 inhibitors‡</td>
</tr>
<tr>
<td>Betrixaban (Bevyxxa)</td>
<td>No information available for concurrent use with P-glycoprotein or CYP3A4 inducer†</td>
<td>Reduce dose with P-glycoprotein inhibitors*</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Avoid concurrent use with P-glycoprotein inducer†</td>
<td>Evaluate P-glycoprotein inhibitors* individually for dose adjustment or avoidance in patients with renal impairment</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>Avoid use with rifampin</td>
<td>Reduce dose for deep venous thrombosis or pulmonary embolism treatment if on select P-glycoprotein inhibitors* (concurrent cyclosporine or antiretroviral medications not evaluated)</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Avoid with combined P-glycoprotein inducer† and strong CYP3A4 inducer†</td>
<td>Evaluate combined P-glycoprotein inhibitor* and moderate CYP3A4 inhibitors‡ for dose adjustment or avoidance in renal impairment</td>
</tr>
</tbody>
</table>

**Note:** Increased bleeding risk with certain medications (e.g., clopidogrel, NSAIDs).

*CYP = cytochrome P450; NSAID = nonsteroidal anti-inflammatory drug.

*—Clarithromycin, dronedarone, itraconazole, ketoconazole, and verapamil.

†—Rifampin.

‡—Clarithromycin, itraconazole, ketoconazole, and protease inhibitors.

Information from references 5 and 9-13.

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**RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN**

<table>
<thead>
<tr>
<th>Best Practices in Hematology</th>
<th>Sponsoring organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not administer plasma or prothrombin complex concentrates for nonemergent reversal of vitamin K antagonists (i.e., outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery).</td>
<td>American Society of Hematology</td>
</tr>
</tbody>
</table>

**Source:** For more information on the Choosing Wisely Campaign, see https://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see https://www.aafp.org/afp/recommendations/search.htm.
Consensus guidelines and a two-dose anticoagulant treatment regimen should be addressed.\textsuperscript{1,20} In patients with atrial fibrillation, the ACCP guidelines recommend assessing bleeding risk for patients with VTE or atrial fibrillation as an essential step to guiding treatment decisions such as the duration of treatment. ACCP risk factors for VTE (e.g., advanced age, cancer, renal or hepatic failure) and an associated scoring system to categorize low (no risk factors), moderate (one risk factor), and high (two or more risk factors) risk should be used to determine treatment decisions.\textsuperscript{1}

The ACCP and AAFP recommend using the HAS-BLED (hypertension, abnormal renal function and liver function, stroke, bleeding, labile INR, elderly [older than 65 years], drugs and alcohol) scoring tool (https://www.mdcalc.com/has-bled-score-major-bleeding-risk) to assess risk of bleeding for patients with atrial fibrillation.\textsuperscript{19,21} Because of the overlap in risk of ischemic stroke and bleeding, patients with the highest risk of ischemic stroke will commonly also have high bleeding risk. Bleeding risk in patients at high risk for ischemic stroke should rarely be used as a reason to withhold anticoagulation for patients with atrial fibrillation.\textsuperscript{21} Risk should be evaluated at each visit and modifiable risk factors, such as alcohol consumption, anemia, anticoagulation control, and use of medications that increase risk of bleeding such as aspirin and nonsteroidal anti-inflammatory drugs, should be addressed.\textsuperscript{21}

### Management of Bleeding

The ACC published an expert consensus decision pathway in 2017 on the management of bleeding for patients taking oral anticoagulants.\textsuperscript{28} Management of bleeding for patients taking vitamin K antagonists depends on the severity of the bleed. For major bleeding (defined as all bleeds associated with hemodynamic compromise, occurring in an anatomically critical site, associated with a decrease of hemoglobin of 2 g per dL [20 g per L] or greater, or requiring transfusion of two units of packed red blood cells or more), the patient should receive supportive care, 4-factor prothrombin complex concentrate, and intravenous vitamin K. The only available 4-factor prothrombin complex concentrate is Kcentra, which is dosed based on INR and body weight. Kcentra contains the vitamin K dependent clotting factors (II, VII, IX, and X) as well as proteins C and S. The patient should also be given vitamin K intravenously to maintain vitamin K-dependent clotting factor levels once the effects of Kcentra have diminished. Kcentra is preferred over a fresh frozen plasma infusion because of its smaller volume, faster infusion rate, and superior effectiveness in INR reduction. For nonmajor bleeding (defined as any bleeding not classified as major) that does not require hospitalization or supportive care, holding vitamin K antagonists and possible administration of vitamin K is recommended depending on INR.

The management of nonmajor bleeding with direct oral anticoagulant therapy typically involves holding the anticoagulant and implementing control measures. Direct oral anticoagulants have half-lives of approximately 12 hours; therefore, holding a dose results in a relatively fast decline of anticoagulant effect. Idarucizumab (Praxbind) is a monoclonal antibody fragment that binds directly to dabigatran, leading to 88% to 98% of patients having concentrations

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct oral anticoagulants should be used as first-line agents for the treatment of venous thromboembolism and the prevention of stroke in patients with nonvalvular atrial fibrillation and a CHA\textsubscript{2}-VASc score of 2 or higher in men and 3 or higher in women.\textsuperscript{20}</td>
<td>C</td>
<td>Consensus guideline on the management of venous thromboembolism and atrial fibrillation</td>
</tr>
<tr>
<td>Bleeding risk assessment should be performed and any modifiable risk factors addressed during each visit.\textsuperscript{1,21}</td>
<td>C</td>
<td>Expert opinion and consensus guidelines</td>
</tr>
<tr>
<td>Vitamin K antagonists should be used for the prevention of stroke in patients with atrial fibrillation with moderate-to-severe mitral stenosis and a CHA\textsubscript{2}-VASc score of 2 or higher in men and 3 or higher in women.\textsuperscript{20,21}</td>
<td>C</td>
<td>Consensus guidelines and a two-dose validation study</td>
</tr>
<tr>
<td>Low-molecular-weight heparin is recommended as the anticoagulant of choice in patients with cancer and venous thromboembolism; however, direct oral anticoagulants may be appropriate in select situations.\textsuperscript{1}</td>
<td>C</td>
<td>Consensus guideline</td>
</tr>
</tbody>
</table>

CH\textsubscript{2}-VASc = congestive heart failure; hypertension; age 75 years or older [doubled]; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65 to 74 years; sex category.

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 https://www.aafp.org/afpsort.
of unbound dabigatran in safe levels within 15 minutes of administration and hemostasis restoration at a median of 11.4 hours. For patients taking dabigatran, idarucizumab is recommended for life-threatening or ongoing bleeding, as well as the need to reverse for emergent procedures.

Andexanet alfa (Andexxa) is a genetically modified variant of factor Xa that binds and sequesters factor Xa inhibitors. Andexanet alfa has been approved to reverse the anticoagulant effects of rivaroxaban and apixaban in patients with life-threatening or uncontrolled bleeding. Optimal dose, duration, need for repeat dosing, and mitigation of thromboembolic risk is yet to be delineated.

VTE Treatment and Cancer

VTE treatment in patients with active cancer is challenging because of the increased risk of VTE recurrence and bleeding related to therapy. Guidelines have recommended LMWH as the anticoagulant of choice for patients with cancer and VTE. Evidence is emerging for the increased use of direct oral anticoagulants for certain patients with cancer. The 2019 National Comprehensive Cancer Network guidelines on cancer-associated VTE include rivaroxaban as a monotherapy option. Apixaban is included as an acceptable alternative for patients who refuse LMWH or who have compelling reasons to avoid LMWH.

The SELECT-D trial evaluated dalteparin with rivaroxaban in patients with active cancer. The study found an absolute VTE recurrence reduction of 7% at six months in favor of rivaroxaban (11% vs. 4%; hazard ratio [HR] = 0.43; 95% CI, 0.19 to 0.99). The major bleeding rate at six months was 4% for dalteparin and 6% for rivaroxaban (HR = 1.83; 95% CI, 0.68 to 4.96). Most of the major bleeding was gastrointestinal, primarily in patients with esophageal or gastroesophageal cancer. Clinically relevant nonmajor bleeding was higher in the rivaroxaban group (13% vs. 4%; HR = 3.76; 95% CI, 1.63 to 8.69). The Hokusai VTE cancer trial evaluated dalteparin with edoxaban in patients with active cancer. The primary outcome (recurrent VTE and/or major bleeding) did not differ between treatment groups (P = .006 for noninferiority). There was a decrease in recurrent deep venous thrombosis in favor of the edoxaban group (3.6% vs. 6.7%; HR = 0.56; CI, 0.32 to 0.97) but an increase in major bleeding in that group (6.9% vs. 4.0%; HR = 1.77; 95% CI, 1.03 to 3.04). Gastrointestinal malignancy was also found to be a risk factor of increased gastrointestinal bleeding when using a direct oral anticoagulant vs. LMWH. Therefore, direct oral anticoagulants should be used with caution in patients with cancer who have a history of gastrointestinal malignancy or bleeding.

This article updates previous articles on this topic by Wigle, et al., and du Breuil and Umland.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms outpatient, anticoagulation, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban, heparin, low-molecular-weight heparin, dalteparin, enoxaparin, patient self-monitor, and INR. The search included meta-analyses, randomized controlled trials, clinical trials, clinical guidelines, and reviews. Also searched were the National Guideline Clearinghouse, Essential Evidence Plus, UpToDate, the Cochrane database, and the Agency for Healthcare Research and Quality Evidence Reports. Search dates: June 28, 2018, and May 2, 2019.

The Authors

PATRICIA WIGLE, PharmD, BCPS, BCACP, FCCP, is a professor in the Division of Pharmacy Practice and Administrative Sciences at the University of Cincinnati (Ohio) and is an ambulatory care clinical pharmacy specialist at The Christ Hospital, Cincinnati.

BRAD HEIN, PharmD, BS, BCPS, is the associate dean for professional education and assessment at the University of Cincinnati and is an internal medicine clinical pharmacy specialist at The Christ Hospital.

CHRISTOPHER R. BERNHEISEL, MD, is the director of the University of Cincinnati/The Christ Hospital Family Medicine Residency Program and is an associate professor in the Division of Pharmacy Practice and Administrative Sciences at the University of Cincinnati (Ohio).
the Department of Family and Community Medicine at the University of Cincinnati.

Address correspondence to Patricia Wigle, PharmD, BCPS, BCACP, FCCP, University of Cincinnati James L. Winkle College of Pharmacy, 3225 Eden Ave., 285 Kowalewski Hall, Cincinnati, OH 45267-0004 (email: patricia.wigle@uc.edu). Reprints are not available from the authors.

References

# LMWH and Fondaparinux for Outpatient Treatment of Venous Thromboembolism in Adults

<table>
<thead>
<tr>
<th>Drug/Dosage</th>
<th>Dosage adjustment in patients with renal impairment</th>
<th>Half-life</th>
<th>Monitoring</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH</strong></td>
<td></td>
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</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>1 mg per kg subcutaneously every 12 hours or 1.5 mg per kg subcutaneously every 24 hours</td>
<td>Enoxaparin 1 mg per kg subcutaneously every 24 hours if CrCl &lt; 30 mL per minute per 1.73 m² (0.50 mL per second per m²)</td>
<td>3 to 6 hours</td>
<td>ASH guide-lines suggest not routinely monitoring anti–factor Xa levels for patients who are obese or those with renal impairment</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>200 units per kg subcutaneously once daily</td>
<td>Use with caution and monitor anti–factor Xa levels in patients with CrCl &lt; 30 mL per minute per 1.73 m²</td>
<td>3 to 5 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Fondaparinux (Arixtra)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weight &lt; 110 lb (50 kg): 5 mg subcutaneously daily</td>
<td>Use with caution in patients with CrCl 30 to 50 mL per minute per 1.73 m² (0.50 to 0.83 mL per second per m²) Contraindicated in patients with CrCl &lt; 30 mL per minute per 1.73 m²</td>
<td>18 hours</td>
<td>Routine monitoring not suggested; if elected for monitoring, use anti–factor Xa levels with fondaparinux as the reference standard for the assay</td>
<td>LMWH and fondaparinux have comparable effectiveness and safety Longer half-life for fondaparinux is advantageous (daily dosing) and potentially troublesome (adverse effects and lack of reversibility) Although not U.S. Food and Drug Administration approved for heparin-induced thrombocytopenia, fondaparinux has been used for the management of these patients</td>
</tr>
<tr>
<td>Weight 110 to 220 lb (50 to 100 kg): 7.5 mg subcutaneously daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &gt; 220 lb: 10 mg subcutaneously daily</td>
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</tr>
</tbody>
</table>

ASH = American Society of Hematology; CrCl = creatinine clearance; LMWH = low-molecular-weight heparin.

Information from:


### Factors to Consider When Dosing Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Usual dosage (assess renal function before beginning direct oral anticoagulant and as clinically indicated)*</th>
</tr>
</thead>
</table>
| **Apixaban (Eliquis)** | Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treat DVT and PE | Prophylaxis for stroke and systemic embolism in nonvalvular atrial fibrillation:  
• 5 mg twice per day  
• Decrease dose by 50% if on 5 mg or 10 mg twice per day and taking combined strong P-glycoprotein inhibitor and strong CYP3A4 inhibitor  
• Avoid in patients taking combined P-glycoprotein and strong CYP3A4 inhibitors if on 2.5 mg twice per day  
• Decrease dose to 2.5 mg twice per day if two of the following: age 80 years or older, body weight ≤ 60 kg (132 lb); serum creatinine ≥ 1.5 mg per dL (114 μmol per L)  
Prophylaxis for DVT or PE:  
• Avoid in patients taking combined P-glycoprotein and strong CYP3A4 inhibitors  
• Reduce recurrence: 2.5 mg twice per day after six months or more of DVT or PE treatment  
• Total hip or knee replacement surgery: 2.5 mg twice per day for 12 days after knee replacement surgery and 35 days after hip replacement surgery  
DVT or PE treatment:  
• 10 mg twice per day for 7 days, then 5 mg twice per day  
• Decrease dose by 50% if on 5 mg or 10 mg twice per day and taking combined strong P-glycoprotein inhibitor and strong CYP3A4 inhibitor  
• Avoid in patients taking combined P-glycoprotein and strong CYP3A4 inhibitors if on 2.5 mg twice per day |
| **Betrexaaban (Bevyxxa)** | VTE prophylaxis in adults hospitalized for an acute medical illness | VTE prophylaxis in at-risk, acutely ill, hospitalized patients: 160 mg with food for first dose, then 80 mg per day with food for 35 to 42 days  
• CrCl 15 to 29 mL per minute per 1.73 m² (0.25 to 0.48 mL per second per m²²): 80 mg with food for first dose, then 40 mg per day with food for 35 to 42 days  
With P-glycoprotein inhibitors:  
• 80 mg with food for first dose, then 40 mg per day with food for 35 to 42 days  
• Avoid use with P-glycoprotein inhibitors and CrCl < 30 mL per minute per 1.73 m² (0.50 mL per second per m²²) |
| **Dabigatran (Pradaxa)** | Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treat DVT and PE | Prophylaxis for stroke and systemic embolism in nonvalvular atrial fibrillation:  
• 150 mg twice per day  
• With P-glycoprotein inhibitors:  
  - dronedarone (Multaq) or ketoconazole and CrCl 30 to 50 mL per minute per 1.73 m² (0.50 to 0.83 mL per second per m²²): 75 mg twice per day  
  - CrCl 15 to 30 mL per minute per 1.73 m²: 75 mg twice per day  
  • Avoid use with P-glycoprotein inhibitors and CrCl < 30 mL per minute per 1.73 m²  
  • Avoid use with CrCl < 15 mL per minute per 1.73 m² with or without drug interaction  
  • Avoid with rifampin  
Prophylaxis for DVT or PE:  
• Total hip replacement surgery: 110 mg on first day, then 220 mg per day for 28 to 35 days  
• Avoid use with P-glycoprotein inhibitor and CrCl < 50 mL per minute per 1.73 m²  
• Avoid with CrCl < 30 mL per minute per 1.73 m² with or without drug interaction  
• Avoid with rifampin  
Reduce recurrence:  
• 150 mg twice per day  
• Avoid with P-glycoprotein inhibitor and CrCl < 50 mL per minute per 1.73 m²  
• Avoid with CrCl ≤ 30 mL per minute per 1.73 m² with or without drug interaction  
• Avoid with rifampin  
DVT or PE treatment:  
• 150 mg twice per day  
• Avoid with P-glycoprotein inhibitor and CrCl < 50 mL per minute per 1.73 m²  
• Avoid with CrCl ≤ 30 mL per minute per 1.73 m² with or without drug interaction  
• Avoid with rifampin  

BMI = body mass index; CrCl = creatinine clearance; CYP = cytochrome P450; DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.  
*—P-glycoprotein inhibitors include amiodarone, azithromycin (Zithromax), clarithromycin (Biaxin), dronedarone, erythromycin, itraconazole (Sporanox), ketoconazole, quinidine, ritonavir (Norvir), saquinavir (Invirase), ticagrelor (Brilinta), and verapamil. CYP3A4 inhibitors include clarithromycin, itraconazole, ketoconazole, and ritonavir. CYP3A4 inducers include carbamazepine (Tegretol), phenytoin ( Dilantin), rifampin, and St. John’s wort.
Patients with hepatic impairment should be dose adjusted. The table below summarizes dosing for patients with hepatic impairment:

### Hepatic Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Impact of Weight</th>
<th>Half-life</th>
<th>Cost</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child-Pugh Class A:</strong> do not need dose adjustment</td>
<td>Refer to usual dosage section for impact of lower weight. Appropriate standard direct oral anticoagulant dosing in patients with a BMI ≤ 40 kg per m² or weight ≤ 120 kg (265 lb) Suggest direct oral anticoagulants not be used in patients with a BMI &gt; 40 kg per m² or weight &gt; 120 kg; if used in these patients, check drug-specific peak and trough levels.</td>
<td>12 hours</td>
<td>$460 for 60 5-mg tablets</td>
<td>Starter pack for initial dosing for treatment of DVT and PE. Coupons available for starter pack and maintenance dosing.</td>
</tr>
<tr>
<td><strong>Child-Pugh Class B and C:</strong> not recommended</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not recommended in patients with hepatic impairment</strong></td>
<td>Appropriate standard direct oral anticoagulant dosing in patients with a BMI ≤ 40 kg per m² or weight ≤ 120 kg Suggest direct oral anticoagulants not be used in patients with a BMI &gt; 40 kg per m² or weight &gt; 120 kg; if used in these patients, check drug-specific peak and trough levels.</td>
<td>19 to 27 hours</td>
<td>$470 for 30 80-mg capsules</td>
<td>Take with food when used for VTE prophylaxis.</td>
</tr>
<tr>
<td><strong>Limited data in patients with hepatic impairment; no specific dosing adjustment recommended</strong></td>
<td>Appropriate standard direct oral anticoagulant dosing in patients with a BMI ≤ 40 kg per m² or weight ≤ 120 kg Suggest direct oral anticoagulants not be used in patients with a BMI &gt; 40 kg per m² or weight &gt; 120 kg; if used in these patients, check drug-specific peak and trough levels.</td>
<td>12 to 17 hours</td>
<td>$420 for 60 150-mg capsules</td>
<td>Do not chew, break, or open capsules. Capsules must be dispensed in original container and cannot be repackaged because of the sensitivity to moisture. May cause dyspepsia.</td>
</tr>
<tr>
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</tbody>
</table>

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†—International Society on Thrombosis and Hemostasis Scientific and Standardization Committee’s Guidance Statements. §—Estimated retail price of brand-name medications based on information obtained at https://www.goodrx.com (accessed April 4, 2019). Actual cost will vary with insurance and by region. §—Amiodarone, clarithromycin, quinidine, ticagrelor, and verapamil have been evaluated with dabigatran and do not require a dabigatran dosage adjustment but should be used concurrently with caution. Evaluate other P-glycoprotein inhibitors on an individual basis.
**Factors to Consider When Dosing Direct Oral Anticoagulants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Usual dosage (assess renal function before beginning direct oral anticoagulant and as clinically indicated)*</th>
</tr>
</thead>
</table>
| Edoxaban (Savaysa) | Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treat DVT and PE. | Prophylaxis for stroke and systemic embolism in nonvalvular atrial fibrillation:  
  - 60 mg daily  
  - Avoid use in patients with CrCl > 95 mL per minute per 1.73 m² (1.59 mL per second per m²)  
  - CrCl 15 to 50 mL per minute per 1.73 m²: 30 mg per day  
  - Avoid use with rifampin  
  DVT or PE treatment:  
  - 60 mg per day after 5 to 10 days of initial parenteral anticoagulant therapy (patients > 60 kg); 30 mg daily after 5 to 10 days of initial parenteral anticoagulant therapy (patients ≤ 60 kg)  
  - If taking certain P-glycoprotein inhibitors or CrCl 15 to 50 mL per minute per 1.73 m²: 30 mg per day  
  - Avoid use with rifampin |
|                   | Not recommended as an acute alternative to unfractionated heparin in patients with PE who present with hemodynamic instability or may receive thrombolysis or pulmonary embolectomy. |                                                                                                           |
| Rivaroxaban (Xarelto) | Reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treat DVT and PE. | Discontinue in patients who develop acute renal failure on rivaroxaban.  
Prophylaxis for stroke and systemic embolism in nonvalvular atrial fibrillation:  
  - 20 mg per day with evening meal  
  - Avoid with combined P-glycoprotein and moderate CYP3A4 inhibitors and CrCl 15 to 80 mL per minute per 1.73 m² (0.25 to 1.34 mL per second per m²)  
  - CrCl 15 to 50 mL per minute per 1.73 m²: 15 mg per day (patients with a CrCl < 30 mL per minute per 1.73 m² were not studied in trials)  
  - Avoid with combined P-glycoprotein inhibitors and CYP3A4 inhibitors and CrCl 15 to 80 mL per minute per 1.73 m²  
  - 10 mg per day after six months or longer of standard anticoagulant therapy  
  - Avoid use with CrCl < 30 mL per minute per 1.73 m²  
  - Avoid with combined P-glycoprotein inhibitors and moderate CYP3A4 inhibitors and CrCl 15 to 80 mL per minute per 1.73 m²  
  - Avoid with combined P-glycoprotein and strong CYP3A4 inhibitors or inducers  
Reduce recurrence:  
  - 10 mg per day after six months or longer of standard anticoagulant therapy  
  - Avoid with combined P-glycoprotein inhibitors and moderate CYP3A4 inhibitors and CrCl 15 to 80 mL per minute per 1.73 m²  
  - Avoid use in CrCl < 30 mL per minute per 1.73 m²  
  - Avoid with combined P-glycoprotein inhibitors and strong CYP3A4 inhibitors or inducers  
DVT or PE treatment:  
  - 15 mg twice per day with food for the first 21 days, then 20 mg per day with food for six months  
  - Avoid with combined P-glycoprotein inhibitors and moderate CYP3A4 inhibitors and CrCl 15 to 80 mL per minute per 1.73 m²  
  - Avoid use in CrCl < 30 mL per minute per 1.73 m²  
  - Avoid with combined P-glycoprotein inhibitors and strong CYP3A4 inhibitors or inducers  
Reduce recurrent DVT and PE, and for DVT prophylaxis (hip and knee replacement) |

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*P-glycoprotein inhibitors include amiodarone, azithromycin (Zithromax), clarithromycin (Biaxin), dexamethasone, erythromycin, itraconazole (Sporanox), ketoconazole, quinidine, ritonavir (Norvir), saquinavir (Invirase), ticagrelor (Brilinta), and verapamil. CYP3A4 inhibitors include clarithromycin, itraconazole, ketoconazole, and ritonavir. CYP3A4 inducers include carbamazepine (Tegretol), phenytoin (Dilantin), and St. John’s wort.†—Amiodarone, clarithromycin, quinidine, ticagrelor, and verapamil have been evaluated with dabigatran and do not require a dabigatran dosage adjustment but should be used concurrently with caution. Evaluate other P-glycoprotein inhibitors on an individual basis. §—Estimated retail price of brand-name medications based on information obtained at https://www.goodrx.com (accessed April 4, 2019). Actual cost will vary with insurance and by region.
CYP3A4 inhibitors include clarithromycin, azole antifungals (e.g., itraconazole, voriconazole), amiodarone, verapamil, and the macrolide antibiotic erythromycin. These medications are strong inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme system, which is responsible for the metabolism (primarily for) several direct oral anticoagulants. Although the FDA and the European Medicines Agency recommend avoiding dabigatran treatment in patients taking strong CYP3A4 inhibitors, the risk of drug interactions is variable and depends on the extent to which dabigatran is metabolized. For patients taking dabigatran and CYP3A4 inhibitors, reducing the dabigatran dose to 110 mg once daily may reduce the risk of drug interactions. However, the evidence for this recommendation is limited. The use of strong CYP3A4 inhibitors with dabigatran is not recommended for patients taking dabigatran at 150 mg twice daily due to the increased risk of bleeding.

**TABLE B**

<table>
<thead>
<tr>
<th>Hepatic dosing</th>
<th>Impact of weight†</th>
<th>Half-life</th>
<th>Cost‡</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Child-Pugh Class A: do not need dose adjustment | Appropriate standard direct oral anticoagulant dosing in patients with a BMI ≤ 40 kg per m² or weight ≤ 120 kg | 5 to 9 hours | $470 for 30 20-mg tablets | Take with food 
Starter pack for initial dosing for treatment of DVT and PE 
Coupons available for starter pack and maintenance dosing |
| Child-Pugh Class B and C: not recommended | Refer to usual dosage section for impact of lower weight |
|                   | Suggest direct oral anticoagulants not be used in patients with a BMI > 40 kg per m² or weight > 120 kg |

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Information from:


