

What's new in anticoagulation for patients with atrial fibrillation?

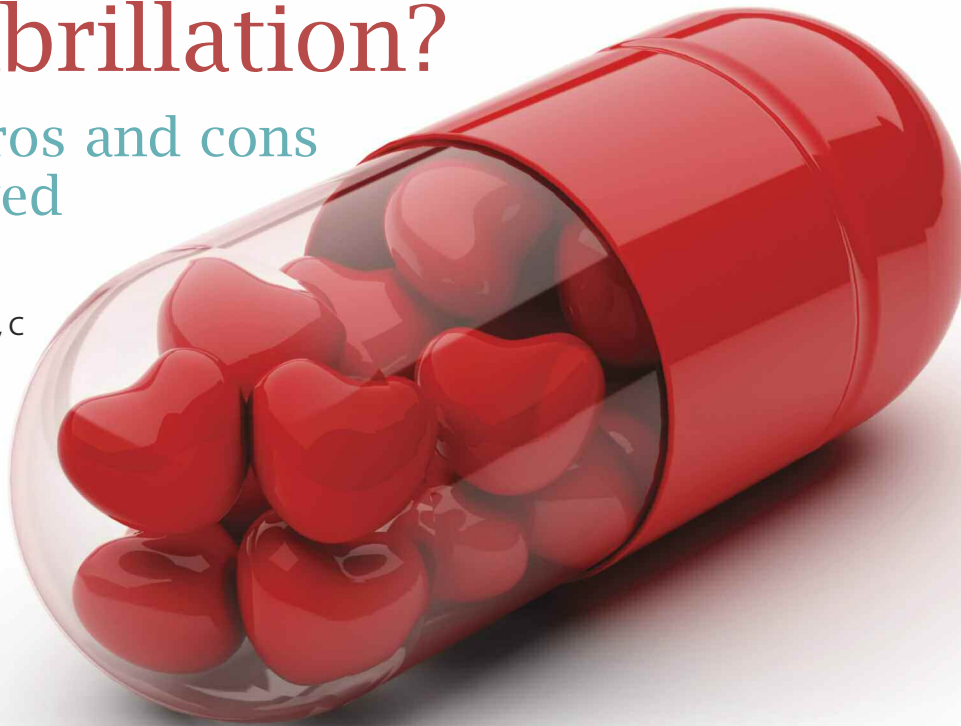
Learn about the pros and cons of recently approved anticoagulants.

By Donna Darcy, MA, RN, ACNS-BC, CMSRN, C

MRS. MURIEL H, age 78, is admitted to the medical-surgical unit with GI bleeding. She has a 5-year history of atrial fibrillation and has been taking warfarin 5 mg P.O. daily because the arrhythmia increases her risk for blood clots and embolic stroke. A community nurse has been visiting her weekly at home to draw blood samples to make sure her prothrombin time and International Normalized Ratio (PT/INR) are in the therapeutic range. Until recently, her values indicated she was being anticoagulated properly.

But 2 weeks before her current admission, Mrs. H's INR rose to 4.3. The nurse called her primary care provider, who decided to keep her on warfarin but lower the dosage to 2.5 mg P.O. daily and retest her in 1 week. Seven days later, the patient's INR had climbed to 8.2, and she reported bright red stools. During her current admission for further evaluation and observation, she is taken off warfarin and placed on bleeding precautions.

What could have caused such a drastic change in Mrs. H's anticoagulation status? Could unidentified dietary changes have played a role in her poor anticoagulation control? Could other factors have contributed directly? Certainly, diet and other factors could have been involved, but a true correlation was never determined for Mrs. H.



Benefits and drawbacks of warfarin

For Mrs. H and others like her, warfarin poses a significant risk due to its volatile and unpredictable effects. Since 1954, it has been used successfully as a potent anticoagulant in the United States. A vitamin K antagonist, it suppresses coagulation by reducing production of clotting factors VII, IX, and X and prothrombin. The drug is approved for prophylaxis and treatment of venous thrombosis and pulmonary embolism, prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, and reduction of thromboembolic events (such as stroke and systemic embolization after myocardial infarction).

However, warfarin therapy poses challenges, particularly in older patients like Mrs. H. Although it's the most widely prescribed oral anticoagulant in the world, its use is complicated by unpredictable dosage requirements to achieve and maintain

optimal anticoagulation. Also, variations in its metabolism among patients contribute to fluctuations in therapeutic response.

The major risk from warfarin is bleeding, as Mrs. H experienced. Warfarin's "black box" warning states the drug "poses a serious and significant health risk due to the potential for major or even fatal bleeding." Healthcare providers must instruct patients taking it to restrict and monitor foods that contain vitamin K or affect vitamin K metabolism. Also, warfarin has many potential drug interactions, necessitates PT or INR monitoring throughout treatment, and requires patients to curtail or modify activities that pose inherent bleeding risks. (See *PT and INR target ranges*.) What's more, because vitamin K is crucial to maintaining bone strength, patients taking warfarin are at risk for bone fracture.

Seeking an alternative

Obviously, warfarin therapy is life-changing for many patients—and

PT and INR target ranges

This table compares typical target ranges for prothrombin time (PT) and International Normalized Ratio (INR) values in patients receiving warfarin to normal values in patients not taking anticoagulants.

Patient population	PT	INR
Patients not taking an anticoagulant	10 to 13 seconds	1.0
Patients therapeutically anticoagulated with warfarin	1.5 to 2 times the control	2.0 to 3.0

medical science has long been looking for safer and easier alternatives.

In light of Mrs. H's GI bleeding, she and her primary care provider decide to review alternative anticoagulant options for preventing thromboembolism in patients with atrial fibrillation. They consider such medications as aspirin, aspirin with clopidogrel, dipyridamole, enoxaparin, and even heparin. However, Mrs. H has seen TV ads for more recently approved anticoagulants and asks the physician if any of these might be right for her.

In recent years, several anticoagulants have been approved to prevent and treat deep vein thrombosis in patients with atrial fibrillation unrelated to a heart valve problem. (See *Anticoagulants at a glance.*)

Dabigatran

Dabigatran (Pradaxa[®]), a direct thrombin inhibitor, was approved by the Food and Drug Administration (FDA) in 2010 to prevent stroke in patients with nonvalvular atrial fibrillation. In clinical trials, it reduced stroke risk 35% more than warfarin did. Patients who take it don't need to have regular blood tests or restrict their diet. But they still are at high risk for bleeding, which can lead to significant and sometimes fatal bleeding events.

Advise patients taking dabigatran to watch for signs and symptoms of active bleeding, such as unusual bruising, pink or brown urine, nosebleed, dizziness or confusion, bleeding gums, and dark, tarry stools. Caution them not to abruptly stop

taking dabigatran; because it has a short half-life, stopping it without an appropriate replacement anticoagulant places patients at markedly high risk for sudden embolic events. Inform patients that if they need to stop taking dabigatran before certain medical and dental procedures, they may have to take other medications to prevent clotting. Instruct them to take dabigatran as prescribed; the typical dosage is 150 mg twice daily taken with or without food, or 75 mg twice daily if they have renal impairment (creatinine clearance below 30 mL/minute).

Advise patients taking these drugs to watch for signs and symptoms of active bleeding.

Caution patients not to break, chew, or open the capsules. Instruct them to keep the medication in its original bottle, tightly closed, and to use it within 60 days of opening the bottle. Teach them to avoid other anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents due to the high risk of bleeding.

Don't give dabigatran to patients also taking P-glycoprotein (P-gp) inhibitors or inducers, such as HIV protease inhibitors, ketoconazole, verapamil, rifampin, or St. John's wort. Caution them that concurrent use of an antacid, such as an H₂ antagonist or a proton-pump inhibitor, may reduce dabigatran effects. Be aware that this drug shouldn't be used in

patients with heart-valve disease or prior heart-valve replacement.

Rivaroxaban

In 2011, the FDA approved rivaroxaban (Xarelto[®]), a factor Xa inhibitor, to reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban can cause serious and fatal bleeding. Teach patients how to recognize both overt and subtle signs of bleeding. Caution them not to stop taking the drug abruptly because this increases the risk for thrombotic events. If they must stop taking it for any reason, such as for planned medical and dental procedures, the physician must prescribe an appropriate alternative anticoagulant.

Be aware that in patients treated with rivaroxaban who receive spinal or other neuroaxial interventions, epidural and spinal hematomas have occurred. Clinicians must weigh the risks and benefits of these procedures in patients receiving rivaroxaban.

Unlike other recently approved anticoagulants, rivaroxaban offers once-daily dosing. Instruct patients to take the drug as prescribed; typical dosage is 20 mg daily taken with the evening meal. Patients with a creatinine clearance of 15 to 50 mL/minute or lower should take 15 mg once daily with the evening meal. Instruct patients who can't swallow tablets to crush the tablet and mix it with applesauce. If the patient requires nasogastric administration, crush the tablet, dilute in 50 mL of water, and administer via a nasogastric or gastric feeding tube. Immediately follow the dose with an enteral feeding. Be aware that rivaroxaban must be used cautiously in patients taking carbamazepine, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, phenytoin, phenobarbital, or rifampin, or St. John's wort.

Apixaban

Apixaban (Eliquis[®]) was approved in 2012 to prevent embolism in pa-

Anticoagulants at a glance

This chart summarizes essential facts about the three newer anticoagulants discussed in this article. (Note: CrCl = creatinine clearance.)

Drug	Classification	Dosage	Major adverse effects	Potential drug and herbal interactions	Patient teaching
Apixaban (Eliquis®)	Factor Xa inhibitor	5 mg twice daily <i>or</i> 2.5 mg twice daily in patients with two or more of the following: • age 80 or older • weight 60 kg (132 lb) or lower • serum creatinine 1.5 mg/dL or higher • itraconazole or ketoconazole therapy	• Bleeding	• Clarithromycin	• Take with or without food. • Don't stop taking drug abruptly. • For missed dose: Take dose right away; take next dose on schedule. Don't double the dose.
Dabigatran etexilate (Pradaxa®)	Direct thrombin inhibitor (anti-IIa)	150 mg twice daily <i>or</i> 75 mg twice daily in patients with CrCl 15 to 30 mL/minute • Don't administer to patients with CrCl below 15 mL/minute.	• Bleeding • Indigestion	• Ketoconazole • Rifampin and other p-glycoprotein inducers	• Take with or without food. • Don't break, chew, crush, or open capsules. • Don't stop taking drug abruptly. • For missed dose: Take dose right away; take next dose on schedule. Don't double the dose.
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	20 mg daily <i>or</i> 15 mg daily in patients with CrCl 15 to 50 mL/minute	• Bleeding	• Carbamazepine • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Phenytoin • Phenobarbital • Rifampin • Ritonavir • St. John's wort	• Take daily with evening meal. • Drug may be crushed or suspended in water and taken in applesauce or by nasogastric tube. • Don't stop taking drug abruptly. • For missed dose, take dose right away; take next dose on schedule. Don't double the dose.

tients with nonvalvular atrial fibrillation. Like rivaroxaban, it prevents clotting by inhibiting factor Xa. Teach patients to take it as prescribed; the typical dosage is 5 mg by mouth twice daily taken with or without food. However, know that

patients with any two of the following should take only 2.5 mg twice daily: age 80 or older, weight 60 kg (132 lb) or lower, or a serum creatinine level 1.5 mg/dL or higher. When apixaban is given concurrently with clarithromycin, itraconazole,

ketoconazole, or zidovudine (strong inhibitors of P-gp), the recommended dosage is 2.5 mg twice daily.

Bleeding is the primary risk of apixaban. Caution patients to avoid taking other medications that prolong clotting times, such as aspirin or

Urge patients to wear medical alert jewelry stating that they're receiving an anticoagulant.

other thrombolytics, nonsteroidal anti-inflammatory agents, and serotonin-norepinephrine reuptake inhibitors. Teach them how to recognize signs and symptoms of blood loss or bleeding. Inform them that no known apixaban antidote or reversal agent exists. Emphasize that missing even one dose or abruptly stopping apixaban without using other anticoagulant coverage puts them at high risk for embolic stroke. Inform them they may need to stop taking apixaban before certain medical and dental procedures and that during this time, they may need to take other medications to prevent clotting.

Developing the plan

When deciding whether Mrs. H should continue taking warfarin or transition to one of the newer anticoagulants, she and her primary care provider consider such factors as her age, medical history, lifestyle, comorbidities, preferences, and financial status. Ultimately, they decide to switch her to a newer anticoagulant.

If your patient is prescribed dabigatran, rivaroxaban, or apixaban, include the following in the teaching plan:

- Explain that this drug increases the bleeding risk. Teach patients how to recognize subtle signs and symptoms of bleeding and what to do if these occur.
- Inform patients that if bleeding occurs, no specific antidote exists.
- Caution them not to stop taking the medication suddenly. Missing even one or two doses greatly increases the embolism risk.
- Inform patients they won't need to have their blood tested frequently or restrict their diet. But point out that it will be harder to assess whether their anticoagulation is adequate.
- Advise them not to take any other medication, herbal remedies, or supplements without discussing it with their primary healthcare provider.

- Urge patients to wear medical alert jewelry stating that they're receiving an anticoagulant.

Comparisons, controversies, and challenges

Do any of the three newer drugs have increased benefits over the others? Although all three showed positive results compared to warfarin in clinical trials, no distinct advantage emerged when compared to each other. Many patients may prefer rivaroxaban's once-daily dosing.

Apixaban, dabigatran, and rivaroxaban remain somewhat controversial. International thrombosis specialists disagree on whether stable patients should be taken off warfarin in favor of a newer anticoagulant. The 2014 guideline from the American College of Cardiology, American Heart Association, and Heart Rhythm Society for management of patients with atrial fibrillation states that patients who are stable on warfarin probably should stay on it. But the guideline authors note that the newer drugs have more predictable effects, cause fewer drug interactions, avoid major dietary effects, and are less likely to cause bleeding than warfarin; consequently, they might be a better alternative for patients with atrial fibrillation who are just starting on anticoagulants. The authors hesitate to recommend one medication over the other, though, because no scientific studies support a decision.

What's more, because these drugs are fairly new, they may pose challenges in terms of safety and efficacy as healthcare providers begin to prescribe them more frequently. Also, they can't be used in patients with heart-valve problems; warfarin is the only agent approved for anticoagulation in this population. In

addition, these drugs are more expensive than warfarin; they may cost \$140 to \$290 per month. ★

Selected references

- Alpert JS. New directions in anticoagulation. *Am J Med.* 2012;125(3):217-8.
- Connolly SJ, Eikelboom J, Joyner C, et al.; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-17.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-51.
- Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation.* 2012;126(20):2381-91.
- Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-92.
- Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation.* 2011;123(13):1436-50.
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2014 April 10.
- Kreuzer J. Update on anti-coagulation in atrial fibrillation. *QJM.* 2011;104(9):747-60.
- Lehne RA. *Pharmacology for Nursing Care*, 8th ed. St. Louis, MO: Saunders Elsevier; 2013.
- Mercaldi CJ, Ciarametaro M, Hahn B, et al. Cost efficiency of anticoagulation with warfarin to prevent stroke in Medicare beneficiaries with nonvalvular atrial fibrillation. *Stroke.* 2011;42(1):112-8.
- Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(1):883-91.
- Verheugt FW. Advances in stroke prevention in atrial fibrillation: enhanced risk stratification combined with newer oral anticoagulants. *Clin Cardiol.* 2013;36(6):312-22.
- Weitz JI, Gross PL. New oral anticoagulants: which one should my patient use? *Hematology Am Soc Hematol Educ Program.* 2012:536-40.

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