Preventing stroke in patients with atrial fibrillation

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Davis, LL. (2013) Preventing stroke in patients with atrial fibrillation. *The Nurse Practitioner, 38(11):* 24-31.

This is a non-final version of an article published in final form in Davis, LL. (2013) Preventing stroke in patients with atrial fibrillation. *The Nurse Practitioner*, 38(11): 24-31. http://dx.doi.org/10.1097/01.NPR.0000435781.73316.9c

Abstract:

Adults with atrial fibrillation are at an increased risk for stroke. New oral antithrombotic agents are now available to help prevent stroke and other thromboembolic events. This article provides an update on factors to consider when determining various treatment options for these high-risk patients in hopes of improving outcomes.

Keywords: anticoagulation | atrial fibrillation | oral antithrombotic agents | stroke prevention

Article:

Atrial fibrillation (AF) is a relatively common cardiac dysrhythmia in adults (see *Identifying AF*). In fact, a 40-year-old adult has about a one in four chance of developing AF in his or her remaining lifetime.[1] The average male and female develop AF at age 66.8 years and 74.6 years, respectively.[1]

Having AF is associated with a two- to threefold increase in mortality.[1] Furthermore, patients with AF are more likely to develop heart failure, dementia, and are four to five times more likely to have an ischemic stroke as compared to those patients without AF.[1] However, the risk of stroke in patients with AF is quite variable, ranging from 1% to 20% annually, depending on comorbidities, age, and whether there is a prior history of stroke.[2]

Figure. Identifying AF
AF is an atrial dysrhythmia characterized by chaotic, asynchronous electrical activity. It results from firing of multiple impulses from numerous ectopic pacemaker sites in the atria. P waves are absent and the ventricular response is irregularly irregular.

FIGURE IS OMITTED FROM THIS FORMATTED DOCUMENT
Source: *ECG Interpretation: An Incredibly Easy Pocket Guide.* Philadelphia, PA: Lippincott Williams & Wilkins; 2006:70.

Types of AF and treatment goals

Traditionally AF has been classified as being acute (lasting less than 48 hours) or chronic. However, a better classification scheme is to distinguish whether the patient with AF has first-detected (first diagnosed) episode or recurrent AF (2 or more episodes). Recurrent episodes can then be further classified into paroxysmal AF (recurrent AF lasting less than 7 days that spontaneously returns to normal sinus rhythm without treatment); persistent AF (recurrent AF lasting more than 7 days requiring treatment to convert to normal sinus rhythm); or the AF may progress to become permanent.[3]

Since patients may have more than one type of chronic AF over their lifetime, they are categorized by with the type that presents most frequently.[3]

Paroxysmal, persistent, and permanent AF are associated with an increased risk of stroke to a similar degree[1]; therefore, one of the most important treatment goals for chronic AF is to prevent stroke and other thromboembolic events. Other major treatment goals (beyond the scope of this article) are to control the ventricular heart rate during episodes of AF and to restore normal sinus rhythm for some patients in persistent AF.

Assessing stroke risk in patients with chronic AF

It is important for nurse practitioners (NPs) to risk stratifying patients with AF to determine who, given the risks and benefits, would be the best match for these agents.[2] One commonly used risk stratification tool recommended by the American Heart Association is the $CHADS_2$ scoring schema[2,4] (see *CHADS2 scoring schema for calculating stroke risk in patients with AF*). The $CHADS_2$ score takes into account stroke risk factors for patients with AF and assigns points for each risk factor. Each letter in the acronym stands for the condition/comorbidity that has been identified as a stroke risk factor. A prior history of stroke or transient ischemic attack earns patients two points (as indicated by the "S_2" in the acronym) as the highest relative risk factor for having a stroke.

Table. $CHADS_2$ scoring schema for calculating stroke risk in patients with AF[2, 4, 6]

Condition or comorbidity	**Points**
Congestive heart failure*	1 point
Hypertension (or treated hypertension)	1 point
Age 75 years or older	1 point
Diabetes mellitus	1 point
Prior stroke or transient ischemic attack	2 points

*The term "congestive HF" has been replaced in many sources with "cardiac HF"

Higher $CHADS_2$ scores equate with a higher likelihood of stroke risk for the patient. For example, a patient with a score of 0 to 1 has a relatively low stroke risk (less than 3% per year).[4] Patients with $CHADS_2$ scores of 2 or 3 have a higher relative risk of stroke (4% to 6% per year).[4] A score of 4 to 5 yields approximately an 8.5% to 12.5% each year,[4] whereas a patient with the maximum score (6) has the highest risk of stroke (~18% per year).[4] Overall, the $CHADS_2$

scoring schema offers clinicians an objective, user-friendly measure for determining which patients are at the highest risk for stroke.

A second, more refined risk stratification instrument, the CHA_2DS_2 VAS_c scoring schema, includes additional risk factors for stroke into the total score (ages 65 to 74 years, female gender, and vascular disease).[5] However, these additional risk factors are less validated and are not currently recommended in the U.S. guidelines.

Table. Stroke prevention treatment recommendations for AF based on $CHADS_2$ score[6]

Score	Stroke risk	Treatment recommendation
0	Low risk	No therapy. If therapy is chosen, aspirin.
1	Moderate risk	Oral antithrombotic therapy is recommended over aspirin or the combination of aspirin/clopiogrel.
≥ 2	High risk	Oral antithrombotic therapy.

Stroke prevention for patients with nonvalvular AF

The American College of Chest Physicians offers evidence-based recommendations for antithrombotic prophylaxis for stroke in patients with nonvalvular AF[6] (see *Stroke prevention treatment recommendations for AF based on $CHADS_2$ score*). According to these recommendations, patients with a $CHADS_2$ score of "0," who are at a very low stroke risk, should not be treated with antithrombotic therapy. For patients who choose therapy, it is suggested that aspirin alone be used rather than antithrombotic therapy or a combination of aspirin and clopidogrel. For patients at an intermediate risk of stroke ($CHADS_2$ score of 1), oral antithrombotic therapy is recommended over aspirin or combination therapy of aspirin and clopidogrel.[2] However, there remains variability in the recommendation for treatment for patients with a $CHADS_2$ score of "1." This group of patients has a relatively moderate risk for stroke and, therefore, requires a more individualized approach to weighing risk versus benefit. Finally, for those at high risk of stroke ($CHADS_2$ score of 2 or greater), antithrombotic therapy is recommended unless contraindicated.[6]

Antithrombotic agents currently available

Vitamin K antagonists.

Warfarin, a vitamin K antagonist, has traditionally been the treatment of choice for stroke prevention in patients with AF. The medication is relatively inexpensive and, until recently, was the most efficacious agent on the market to prevent stroke in patients with AF. However, there are two major drawbacks that arise with warfarin use. The first is that warfarin is frequently underutilized by providers and patients, in part, due to the risk of bleeding, especially in older adults. The second challenge relates to the difficulty in keeping the medication in the desired therapeutic range. It is estimated that only about 58% of those patients who are taking warfarin are within the desired therapeutic range.[7] Reasons for this difficulty include the pharmacologic properties of the drug (a narrow therapeutic window, unpredictable anticoagulant effects, genetic variability in metabolism, and multiple drug-drug and drug-food interactions) and the inconvenience of monitoring of drug levels.[7] Subtherapeutic drug levels place the patient at an

increased risk for stroke, whereas drug levels above the therapeutic range place the patient at risk for bleeding.

Table. Antithrombotic treatment options for stroke prevention in nonvalvular AF[8-11]

Antithrombotic agent/ Mechanism of action	**Dosing information**	**Key nursing implications**
Warfarin Vitamin K antagonist	• Peak effect 72 to 96 hours. • Mean half-life 40 hours. • Dose varies (dose is individualized). Typically, the starting oral dose is between 2 to 5 mg once daily, in the evening. • No dosage adjustment with kidney impairment.	• Requires ongoing lab monitoring. INR goal: 2.0 to 3.0 for nonvalvular AF. • Antidote: Vitamin K.
Dabigatran direct thrombin inhibitor (also known as a factor IIa inhibitor	• Peak effect 1 to 2 hours. • Half-life 12 to 17 hours. • Patients with CrCl > 30 mL/minute the dose is 150 mg orally twice daily • Patients with CrCl 15 to 30 mL/minute the dose is 75 mg orally twice daily • No dosing information is available if CrCl < 15 mL/min or if patients are on dialysis.	• Requires no lab monitoring. • No specific antidote. • Patients must be able to swallow capsules.
Rivaroxaban Direct factor Xa inhibitor	• Peak effect 2 to 4 hours. • Half-life 5 to 9 hours; 11 to 13 hours for older adults or those with CKD. • Patients with CrCl > 50 mL/minute the oral dose is 20 mg daily with the evening meal • Patients with CrCl 15 to 50 mL/minute the oral dose is 15 mg daily with the evening meal • Do not use if CrCl < 15 mL/min. • Stop the drug if the patient develops acute renal failure.	• Requires no lab monitoring. • No specific antidote. • Administer with food to increase bioavailability.
Apixaban Direct factor Xa inhibitor	• Peak effect 3 to 4 hours. • Half-life 12 hours. • Recommended oral dose is 5 mg twice daily for most patients. • Recommended oral dose is 2.5 mg twice daily for patients with at least two of the following: age ≥ 80 years, body weight of ≤ 60 kg, or serum creatinine of ≥ 1.5 mg/dL. • No dosing information if CrCl < 15 mL/min or if on dialysis.	• Requires no lab monitoring. • No specific antidote.

CrCl = Creatinine Clearance; INR = International Normalized Ratio

New antithrombotic agents.

Three alternative antithrombotic agents to warfarin have recently been approved by the USFDA; dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) (see *Antithrombotic treatment options for stroke prevention in nonvalvular AF*).[8–11] The FDA approved the new agents for patients with nonvalvular AF (AF not caused by valvular heart disease or those with mechanical heart valves). All others who need chronic anticoagulation for stroke prevention should be treated with warfarin.

All three alternative agents have been studied in comparison to warfarin and performed the same or better than warfarin in relation to efficacy and safety. In an indirect comparison of the new medications, as compared to warfarin, all offered an advantage of fewer strokes and systemic emboli and provided an additional 10% reduction in mortality.[7] Furthermore, as compared to warfarin, all three agents are associated with lower bleeding rates (including fewer hemorrhagic strokes, intracranial hemorrhages, and major bleeds).[7]

Dabigatran, the first FDA-approved alternative to warfarin, is a direct thrombin inhibitor (factor IIa inhibitor). This medication is a prodrug that peaks within a few hours and is eliminated primarily by the kidneys.[8] Dabigatran has a half-life of approximately 12 to 17 hours in patients with a normal creatinine clearance (CrCl).[8] The prescribed daily oral dose is based on the patient's CrCl.[8] Do not prescribe for those with severe kidney impairment (CrCl < 15 mL/min).[8]

Rivaroxaban, the second FDA-approved alternative to warfarin, is a direct factor Xa inhibitor. Like dabigatran, rivaroxaban peaks fairly quickly. This medication has a half-life of approximately 5 to 9 hours in healthy adults (ages 20 to 45 years) and is 50% higher in older adults or in those with chronic kidney disease (CKD) (11 to 13 hours).[9] However, unlike dabigatran, rivaroxaban is only partially eliminated by the kidneys (~33%).[9] The prescribed, once-daily oral dose is based on the patient's CrCl.[9]

Apixaban, the third FDA-approved alternative to warfarin, is also a direct factor Xa inhibitor. The medication, similar to the other two antithrombotic agents, peaks within a few hours and has a half-life of approximately 12 hours.[10] However, apixaban is primarily eliminated through the intestines and only partially eliminated by the kidneys (27%)[10]; it is prescribed twice daily at 5 mg. Per the packet insert, if the patient has at least two of the following: age > 80 years, body weight of < 60 kg, or a serum creatinine of > 1.5 mg/dL, the recommended dose is 2.5 mg twice daily.[10]

Contraindications to chronic antithrombotic therapy

Contraindications to warfarin include active bleeding or conditions that place the individual at high risk for major bleeding (blood dyscrasias, recent or anticipated surgery of the central nervous system, spinal puncture, other diagnostic/therapeutic procedures that have the potential for uncontrollable bleeding, or major regional/lumbar block anesthesia). Additional contraindications to warfarin include a known hypersensitivity to warfarin, malignant hypertension, pregnancy (except in the case of women who have mechanical heart valves), and use in unsupervised patients who have the high potential for nonadherence.[11]

Contraindications to the newer antithrombotic agents include the following: active bleeding or the potential for major bleeding, known hypersensitivity to any of the medications that are being considered, those with prosthetic valves or those with hemodynamically significant valvular heart disease, women who are pregnant or breastfeeding, those with severe kidney failure (CrCl < 15 mL/min) or advanced liver disease (impaired baseline clotting function), and unsupervised patients who have the high potential for nonadherence.[8–10]

Safety concerns of antithrombotic agents

The primary safety concern for any antithrombotic agent is major bleeding. Major bleeding may be classified as fatal bleeds, hemorrhagic stroke, intraocular bleeds, and gastrointestinal bleeds. In general, however, all of these bleeding events combined occur infrequently (~2% to 4% per year) for both warfarin and the newer agents.[7] Based on data from the clinical trials, hemorrhagic strokes occur approximately 0.10% to 0.47% per year, which was less likely in patients who have received the newer agents in the clinical trials (0.10% to 0.26%/year).[7]

Patients who are at highest risk for bleeding should be identified in advance of starting antithrombotic therapy. For example, certain risk factors for bleeding are also absolute or relative contraindications to starting therapy at all. These include the following: a history of bleeding (greatest risk factor for bleeding) or a predisposition for bleeding, abnormal liver or kidney disease, uncontrolled hypertension, concomitant drug or alcohol use, reduced platelet count/function, excessive fall risk, and malignancy.[12,13] Other risk factors for bleeding, however, are also risk factors for having a stroke (prior history of stroke, age of over 65 years, and a history of hypertension).[12,13] For example, research has shown that the higher a patients' $CHADS_2$ score is and the older a patient is, the higher the likelihood there is of bleeding.[14] This situation creates a challenge for the clinician as to whether to start antithrombotic therapy. However, it is important for the clinician to keep in mind, when considering risk-benefit ratios, the likelihood of stroke is greater than the likelihood of bleeding in many patients with AF. Thus, the clinician should openly discuss the risks/benefits of antithrombotic therapy with each individual patient to determine the best treatment plan for stroke prevention.[5,7]

Management of bleeding

Management of bleeding needs to be taken into consideration in advance of starting any chronic antithrombotic therapy. Warfarin has a specific antidote (vitamin K).[11] However, at this time, none of the newer agents have specific antidotes.

Dabigatran is partially dialyzable, but the data are limited.[8] However, the other two new agents are not expected to be dialyzable. The use of activated charcoal to reduce absorption of rivaroxaban and apixaban may be considered for cases of overdosage.[9,10] Furthermore, “universal antidotes” for factor Xa inhibitors (rivaroxaban and abixaban) are currently in phase 2 drug development studies.[16]

A temporary discontinuation of therapy for the new agents may suffice for management of minor bleeds due to the relatively short half-life (ranging from 2 to 4 hours). If discontinued, approximately half of the medication will be out of the body within a few hours.

Beyond the use of an antidote (for warfarin), treatment for major bleeding with warfarin includes: stopping the agent, applying direct pressure to the bleeding site (if the site is compressible), and administering I.V. fluids and blood products as needed (fresh frozen plasma 2 to 4 units, red blood cells, prothrombin complex concentrate, and/or activated Factor VII).[11] Management of major bleeding for the newer agents, however, is less well established. The use of procoagulant reversal agents (prothrombin complex concentrate, activated prothrombin complex, or recombinant Factor VIIa) may be helpful, but data are limited, as these have not been evaluated in clinical studies.[15]

Patient education

In general, as with any medication that has the potential to increase the risk of bleeding, all patients should be made aware of signs and symptoms of bleeding (unusual bleeding from nose or gums, heavier than normal menstrual bleeding, red or brown urine, red or black colored stools, hemoptysis, vomiting blood or coffee ground emesis, or unusual bruising or discoloration on the skin).[8–11] If the patient experiences any of these signs or symptoms, especially if severe, they should notify their healthcare provider immediately or seek medical attention right away.

Specific patient education for newer agents.

Because of the relatively short half-life of the new antithrombotic agents, it is very important for patients to not miss a dose, therefore, leaving them unprotected for stroke prevention. It is also important to instruct patients not to stop their medications abruptly, due to the increased risk of stroke (as a result of subtherapeutic drug levels). If they anticipate stopping the medication, they should consult with their healthcare provider first.

Patients should be advised not to double up on doses in the event of a missed dose. In the case of dabigatran, if the patient realizes that they missed a dose soon after the “usual” time they take the medication, they may take the missed dose as long as they can space the next dose out by at least 6 hours.[8] The packet insert for apixaban, the other twice-daily medication, recommends taking the missed dose as soon as possible on the same day.[10] As with dabigatran, apixaban should not be doubled to make up for the missed dose.[8,10]

It is important to remind patients taking dabigatran to not to open, cut, or crush the capsules. If the pellets are taken without the capsule shield, the oral bioavailability is increased by 75%, which would place the patient at an increased risk of bleeding.[8] Therefore, patients must be able to swallow the capsules if prescribed dabigatran. In addition, due to the possibility of degradation, the capsules should not be taken out of the pill container or blister pack until they are ready to swallow the capsule.[8] This means medication boxes for ease of administration should not be prefilled by others due to the possible degradation of the capsules. Patients should also be advised to use all the capsules within 4 months of opening the bottle.[8]

Rivaroxaban may be crushed and taken with a small amount of applesauce followed by food for patients who are unable to swallow the tablet whole.[9] For those with a nasogastric tube or a gastric feeding tube, after confirming tube placement, the tablet may be crushed and mixed with water and administered via the tube.[9]

Drug-food and drug-drug interactions

There are many drug-drug and drug-food interactions associated with warfarin. Fewer of these interactions exist with the newer antithrombotic agents. The only known food interaction with a newer agent involves rivaroxaban (15 or 20 mg doses). This agent should be given with food (the evening meal) to maximize the bioavailability of the drug.[9] The other two newer agents may be taken with or without food.[8,10]

Some important drug-drug interactions with the newer agents exist, specifically with CYP3A4 and P-glycoprotein (P-gp) transporter inhibitors and inducers. The packet inserts for the newer agents provide specific drug-drug interactions for each of the medications.[8–10] For example, for rivaroxaban and apixaban (the factor Xa inhibitors), inducers of CYP3A4 and P-gp are known to decrease the exposure to the medication, thus, increasing the risk of stroke; therefore, concomitant use should be avoided.[9,10] These agents, as listed on the packet inserts, include rifampin, carbamazepine, phenytoin, and St. John's wort. The packet insert for dabigatran, the other new antithrombotic agent, specifies that coadministration with rifampin should also be avoided.[8]

Likewise, strong inhibitors of CYP3A4 and P-gp may increase the risk of bleeding when given concurrently with the newer agents. Examples of these agents include ketoconazole, itraconazole, ritonavir, and clarithromycin. If concurrently administered with apixaban, a lower dose should be prescribed (2.5 mg twice daily).[10] Likewise, the dose of dabigatran should be decreased (75 mg twice daily) if given to patients with moderate renal impairment (CrCl of 30 to 50 mL/min) and if given with dronedarone or systemic ketoconazole.[8] Concurrent administration of any of these agents with rivaroxaban, however, should be avoided all together.[9]

Finally, as with warfarin, any of the new antithrombotic agents taken concurrently with other agents that alter coagulation (aspirin, antiplatelet agents, chronic nonsteroidal anti-inflammatory drug use, heparin, and fibrinolytics) can increase the risk of bleeding.[8–11]

Discontinuation of therapy for surgery or other procedures

In general, the newer antithrombotic agents should be stopped within 24 to 48 hours of elective surgery. All three agents should be discontinued at least 48 hours prior to elective surgery or invasive procedures that have a moderate-to-high risk of clinically significant bleeding.[8–10] Longer drug-free intervals (3 to 5 days) should be considered for patients who have an altered CrCl (CrCl less than 50 mL/min).[8–10] However, the surgeon should be consulted to discuss specific patient situations.

For elective surgery or invasive procedures that carry a low risk for bleeding, the medications should be stopped 24 hours prior to surgery.[8–10] After surgery, the medications should be

resumed when hemostasis is obtained to avoid an extensive drug-free interval, which places the patient at risk for stroke. Most dental procedures may be performed safely on full-dose medications. However, advise patients to give the dentist the list of their current medications prior to the procedure.

Implications for advance practice registered nurses

NPs and other advance practice registered nurses should consider the risks and benefits when deciding which therapy to prescribe for stroke prophylaxis in patients with nonvalvular AF. The newer antithrombotic agents offer several advantages over warfarin and are more efficacious in preventing stroke and systemic emboli as compared to warfarin in addition to a reduction in mortality.[7,17] The newer agents are associated with a lower likelihood of having a hemorrhagic stroke (by 40% to 70%), intracranial hemorrhage (~50%), and less major bleeding as compared to warfarin.[7,17] The newer agents have a more rapid onset of action, a shorter half-life, and are more convenient to prescribe (no dose adjustments or need for international normalized ratio [INR] monitoring).[7,17,18]

There are, however, disadvantages to having patients take the newer agents as compared to warfarin. Newer medications are typically associated with a substantial increase in cost as compared to medications off patent. In addition, the newer medications do not have a specific antidote (whereas warfarin does). Another downside to the newer agents is that they have a much shorter half-life as compared to warfarin, so if a patient inadvertently misses a dose, they are much more likely to have a stroke as compared to missing a dose of warfarin.[8–10,17,18] In addition, some patients who have been on warfarin for an extended period of time do not want to "let go" of the lab monitoring. Finally, as with any new class of medications that have obtained FDA approval, some adverse reactions may not be reported until the medications have been on the market for a longer period of time.

When to use which agents.

In general, the most important take-home message for preventing stroke in patients with nonvalvular AF is to treat them with any antithrombotic therapy if they have a $CHADS_2$ score of 1 or more, unless contraindicated. Beyond this general rule, there are a few other tips for deciding which agent to place patients on.

When treating patients who are not managing well on warfarin, the consensus is to switch them to an alternative agent, as per the prescribing information of the newer agent. This can be done once the INR is less than 2.0 for dabigatran and apixaban, and less than 3.0 for rivaroxaban.[8–10]

When treating patients who are on warfarin and doing well, there are two schools of thought. Some experts advise to leave them alone if they are in the therapeutic range most of the time, and they are not experiencing any adverse reactions.[7] Other experts say to convert all of those (who can afford it) to the newer agents due to the increased efficacy and safety profile.[7]

When treating a third group of patients, those naive to any type of antithrombotic therapy, there are also two schools of thought. Some experts say put any patient who can afford it on the newer

agents; others say it does not matter which agent is used as long as they are on some type of stroke prophylaxis[7,17]; therefore, it is important to discuss the pros and cons of each type of therapy with the patient and their family.

When deciding which of the newer agents to choose, indirect comparisons provide insight into subtle, but unique advantages for each of the three medications.[7,17,18] Dabigatran has the best efficacy (for stroke prevention) as compared to the other two agents.[7,17] Apixaban has the best safety profile (less bleeding).[7,17] Rivaroxaban provides more convenient dosing: once a day as opposed to twice daily with the other two agents. Finally, for patients with CKD, rivaroxaban and apixaban have less renal excretion as compared to dabigatran.

Optimize patient outcomes

NPs should be knowledgeable about how to risk stratify patients with AF to determine who needs stroke prophylaxis. For those patients who need therapy, there are new treatment options that are available. NPs need to weigh the pros and cons of using new therapy versus conventional treatment with warfarin in order to optimize patient outcomes.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6–e245.

2. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43(12):3442–3453.

3. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused update incorporating the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol*. 2011;57(11):e101-e198.

4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864–2870.

5. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137(2):263–272.

6. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e531S–e575S.

7. Granger CB, Armaganijan LV. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. *Circulation*. 2012;125(1):159–164.

8. Pradaxa®[package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; Revised April 2013.

9. Xarelto®[package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; Revised March 2013.

10. Eliquis®[package insert]. Princeton, NJ: Bristol-Myers Squibb Pharma Co.; Issued December 2012.

11. Coumadin®[package insert]. Princeton, NJ: Bristol-Myers Squibb Co.; Revised October 2011.

12. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151(3):713–719

13. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093–1100.

14. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ*. 2013;185(2):E121–E127.

15. Pollack CV Jr.. New oral anticoagulants in the ED setting: a review. *Am J Emerg Med*. 2012;30(9):2046–2054.

16. Portola Pharmaceuticals. Portola initiates phase 2 study of PRT4445, universal antidotes for factor Xa inhibitor anticoagulants [press release]. December 10, 2012.

17. Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2012;60(8):738–746.

18. Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. *Am Fam Physician*. 2013;87(8):556–566.