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Reducing Stroke Risk in Patients With Atrial Fibrillation

Atrial fibrillation (AF), the most frequent type of arrhythmia requiring medical intervention, is defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[1,2] Seventy percent of patients with AF also have preexisting heart disease, including coronary artery disease (CAD), hypertensive heart disease, valvular heart disease, and hypertrophic cardiomyopathy.[3] It has been estimated that as many as 3 million people have AF in the United States.[4] The risk of AF doubles each decade of life starting at age 50, and this risk continues through age 90.[5,6] The median age of those affected is 75.[2] Patients with AF have a fivefold increase in the risk of stroke,[7,8] primarily related to cardioembolism.[1,8,9] Following a stroke, patients with AF experience increased mortality, stroke recurrence rates, and lengths of hospital stay, as well as lower hospital discharge rates, relative to stroke patients without AF.[8,10] The 1-year mortality rate of AF-associated stroke is 50%.[7,8] One of the greatest challenges in managing patients with AF is reducing the risk of stroke. Despite the recommendation that patients with AF who are at moderate or high risk of stroke receive chronic anticoagulation, most patients do not receive such therapy.[11] This *Current Medical Evidence* discusses the prophylactic use of anticoagulants in patients with AF.

This CME-certified activity is based on a multidisciplinary expert roundtable held on April 19, 2011.

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Activity Overview

Atrial fibrillation (AF), which affects more than 2.3 million patients in the United States, is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function; it is the most common arrhythmia requiring medical care. Cardioembolism due to AF accounts for about one in six strokes and is a potentially preventable cause of stroke-related disability, dementia, and death. Current guidelines recommend that AF patients at moderate to high risk of stroke be started on chronic anticoagulation with a vitamin K antagonist. However, despite overwhelming evidence of its benefit, anticoagulant prophylaxis in patients with AF is significantly underused, to the detriment of patient health. This activity reviews the evidence supporting current guidelines for anticoagulant use, including a comparison of stroke prevention efficacy versus risk of hemorrhage. The effective use of patient stratification schemes for optimizing therapeutic approaches is also discussed, as are the currently approved options for oral anticoagulation and therapeutic options that are in development.

Target Audience

This activity has been designed to meet the educational needs of cardiologists, internists, extended members of the cardiac care team, and other providers involved in the care of patients diagnosed with AF.

Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Review current guidelines for the management of AF
- Apply risk-assessment strategies when managing patients with AF
- Optimize clinical management plans for the prevention of stroke in patients with AF that utilize risk-benefit assessments of current and emerging anticoagulant therapies

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Reducing Stroke Risk in Patients With Atrial Fibrillation

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This newsletter contains discussions of the following investigational agents: apixaban, rivaroxaban, and edoxaban

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Case Introduction

A 66-year-old male with a known history of hypertension, hyperlipidemia, and type 2 diabetes mellitus presents with symptoms of irregular palpitation, shortness of breath, and fatigue. He claims that the symptoms developed over the past week. An electrocardiogram (ECG) and transthoracic echocardiogram are ordered. Based on the results, a diagnosis of AF is made. Calculating a $CHADS_2$ (congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke or transient ischemic attack) score of 2, you discuss therapeutic options with the patient and prescribe warfarin. You explain the need for careful monitoring of the international normalized ratio (INR) range to balance efficacy and risk, and schedule a follow-up visit to titrate INR.

Clinical Assessment and Risk Stratification

The updated 2011 AF guidelines from the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and Heart Rhythm Society (HRS) are an important resource for the optimal diagnosis and management of patients with AF.[1] According to these guidelines, the first step in managing a patient suspected of having AF is performing a thorough evaluation of his or her medical condition. Although the precise pathophysiology of AF is unknown, it is often triggered outside the atrium in areas such as the pulmonary veins.[12] Though less common, noncardiac causes of AF include electrolyte depletion, acute infections, lung carcinoma, pulmonary embolism, and thyrotoxicosis.[13] Therefore, the basic assessment of patients with AF includes a thorough medical history, physical examination, laboratory testing (focusing on thyroid, renal, and hepatic function and including measurement of serum electrolytes) and an ECG.[1] AF is identified by the replacement of P waves with rapid oscillations of variable timing, shape, and amplitude in the ECG. A thorough evaluation identifies the cause of AF, determines any contributing medical factors, and assesses the patient's tolerability to, or history of, prior treatment for AF. More specific tests can also be used to gather information not available from traditional ECG results.[1]

Based on the clinical evaluation, AF may be classified as either paroxysmal or nonparoxysmal. Paroxysmal AF refers to episodes that spontaneously end within a 7-day period, whereas nonparoxysmal AF has episodes lasting longer than 7 days that do not spontaneously terminate.[14] Nonparoxysmal AF can be further divided into persistent and permanent. Persistent AF is terminated through cardioversion; permanent AF is nonresponsive to cardioversion.[14] An important characteristic of AF is that the greater the frequency of occurrence, the greater the likelihood of future episodes.[15,16]

Once AF is diagnosed, the current guidelines call for rate or rhythm control and prevention of thromboembolism.[1] Rate and rhythm control are beyond the scope of this monograph, but a detailed discussion is available in the current guidelines.[1] All patients with AF should be considered for antithrombotic therapy.

The patient's individual risk of stroke plays an important role in therapeutic decisions, especially in the choice of anticoagulant.[1] One of the most frequently used tools to assess stroke risk is the $CHADS_2$ tool.[17] In 2001, Gage et al published the first paper using the $CHADS_2$ tool, which was developed by expert consensus and based on both the Stroke Prevention and Atrial Fibrillation (SPAF) risk-classification scheme and the Atrial Fibrillation Investigators (AFI) risk-assessment scheme.[18] A stroke risk score is obtained with $CHADS_2$ by adding the total number of risk factors present in a patient (Table 1).[18,19] Among a group of 1,733 Medicare beneficiaries between the ages of 65 and 95, the stroke rate per 100 patient-years in patients with nonvalvular AF who had the lowest $CHADS_2$ stroke risk score (0) was 1.9, and the stroke rate per 100 patient-years in AF patients with the highest $CHADS_2$ risk score (6) was 18.2.[18] Furthermore, stroke rate increased by a factor of 1.5 with every 1-point increase in $CHADS_2$ score.[18]

Other stroke-risk stratification schemes are also available, and it is difficult to determine which single tool is the most accurate at predicting overall stroke risk.[20] A study of five stroke risk tools ($CHADS_2$, SPAF, AFI, Framingham, and American College of Chest Physicians) was designed to determine which scheme was the most accurate at predicting stroke.[17] The study used pooled data from 2,580 patients who participated in several large prospective studies on the effects of aspirin in preventing thromboembolism in patients with nonvalvular AF. The authors concluded that all five tools were able to successfully identify patients with a low risk

of stroke. The $CHADS_2$ tool was found to be more sensitive than the others in identifying high-risk patients, as evidenced by the number of strokes per 100 patient-years; patients identified as high risk through $CHADS_2$ had a rate of 5.3 strokes per 100 person-years compared with stroke rates ranging from 3.0 to 4.2 strokes per 100 patient-years for the other tools.

Table 1. *$CHADS_2$ risk assessment tool: scoring and stroke rate by score.*[18,19]
Reprinted from *Vasc Health Risk Manag* 6, Maegdefessel L, et al. New options with dabigatran etexilate in anticoagulant therapy, 339-349. Copyright 2010, with permission from Dove Medical Press Ltd.

C:	Congestive heart failure	= 1 point
H:	Hypertension (systolic >160 mmHg)	= 1 point
A:	Age >75 years	= 1 point
D:	Diabetes	= 1 point
S:	Prior transient ischemic attack or stroke	= 2 points

$CHADS_2$ Score	Adjusted Stroke Rate (%) (95% Confidence Interval)	
0	1.9 (1.2–3.0)	Low Risk
1	2.8 (2.0–3.8)	
2	4.0 (3.1–5.1)	Moderate Risk
3	5.9 (4.6–7.3)	
4	8.5 (6.3–11.1)	High Risk
5	12.5 (8.2–17.5)	
6	18.2 (10.5–27.4)	

Anticoagulation

Warfarin is the anticoagulant recommended for patients who have a high risk of stroke or who have several moderate risk factors for stroke, including hypertension, diabetes, age 75 or over, left ventricle ejection fraction up to 35%, or heart failure ($CHADS_2 \geq 2$).[1] In AF patients with a low risk of stroke ($CHADS_2 \leq 1$), aspirin may be used.[1]

Warfarin is far more effective than aspirin in reducing the occurrence of stroke.[21,22] The effectiveness of warfarin in patients with AF was established in a study that found warfarin superior to aspirin or placebo in preventing thromboembolism.[21] Following this study, it has generally been accepted that warfarin is the more effective therapy for the prevention of thromboembolism in patients with AF who are at a moderate to high risk of stroke.[1,23] This conclusion was supported by a meta-analysis that also found warfarin to be more effective than aspirin in preventing stroke.[22]

This meta-analysis compared the efficacies and risks of warfarin and aspirin and found that patients taking adjusted-dose warfarin (five trials, 2,837 participants) had a relative risk reduction for stroke of 36% (confidence interval [CI], 14% to 52%) compared with aspirin.[22] These patients also had more than twice as many intracranial hemorrhages than those who received aspirin (17 of 2,319 patients receiving warfarin versus 7 of 3,119 patients receiving aspirin; relative risk, 2.1 [CI, 1.0 to 4.6]). Major extracranial hemorrhage increased in patients who received warfarin relative to what was seen in those who received aspirin (relative risk, 2.0 [CI, 1.2 to 3.4]; absolute risk increase, 0.2% per year).[22] Therefore, the safe and effective use of warfarin balances efficacy in preventing thromboembolism while reducing risks for hemorrhage.

Studies have demonstrated that stroke risk reduction for AF patients is maximal at an INR of 2.0 to 3.0, whereas the risk of intracerebral hemorrhage increases above an INR of 3.5 but does not decrease below an INR of 2.0.[24-26] Therefore, it has been recommended that the balance between adequate anticoagulation and lower bleeding risk is best achieved with an INR range of 2.0 to 3.0 in AF patients under 75 who are at a high risk of stroke.[1,27] For patients over 75 who have a high risk of bleeding, an INR target range between 1.6 and 2.5 is appropriate.[1]

Despite these recommendations, many patients do not achieve or maintain this optimal INR range. A retrospective analysis of 67 studies investigating anticoagulation control published between 1987 and 2005 found that patients achieved a therapeutic INR only 64% of the time.[28] Furthermore, studies showed that patients maintained a therapeutic INR less frequently in community practices (57%) than did patients in anticoagulation clinics (66%) or clinical trials (66%).[28] Common causes for low INR values include nonadherence to therapy, interruptions in therapy for medical procedures, and recent dose reductions.[29] The inability to maintain a therapeutic INR range at least 70% of the time has been associated with a greater incidence of thromboembolic events, including stroke.[29-31]

It has been recommended that, when initiating warfarin therapy, clinicians start with a daily dose of 5 mg for the first 1 to 2 days, with subsequent dosing based on INR values.[32] Monitoring of INR values should occur after two to three doses at the beginning of therapy.[32] Once a stable dose has been found, INR values should be measured at least once every 4 weeks.[32] In patients with serious or life-threatening bleeding and an elevated INR, a combination of holding warfarin therapy and administering vitamin K, fresh

Table 2. *Management of bleeding events in patients on warfarin.*[32]

Ansell J, Hirsch J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:160S-198S. Reproduced with permission from the American College of Chest Physicians.

INR more than therapeutic range but <5.0; no significant bleeding	Lower or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required (**Grade 1C**).
INR ≥5.0, but <9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), particularly if at increased risk of bleeding (**Grade 1C**). If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg po) can be given (**Grade 2C**).
INR ≥9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h (**Grade 1B**). Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with FFP, PCC, or rVIIa, depending on the urgency of the situation; vitamin K can be repeated q12h (**Grade 1C**).
Life-threatening bleeding	Hold warfarin therapy and give FFP, PCC, or rVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR (**Grade 1C**).
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously (**Grade 1A**).

INR, international normalized ratio; FFP, fresh frozen plasma; PCC, prothrombin complex concentrates; rVIIa, recombinant activated factor VII

frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa is recommended (Table 2).[32] Drugs, diet, and various disease states can alter the pharmacokinetics of warfarin. Therefore, it is important that clinicians identify any prescription or nonprescription medications their patients are receiving, as well as any supplements that they are taking.[32] The INR should be measured more frequently than the usual 4-week interval when virtually any drug, dietary supplement, or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin.[32] For example, drugs such as cholestyramine can reduce the anticoagulant effect of warfarin by reducing its absorption. Some drugs may potentiate the anticoagulant effect of warfarin by inhibiting its clearance, whereas other drugs may inhibit the anticoagulant effect by enhancing its clearance.[32] For a more detailed discussion, see Ansell et al, 2008.[32]

Despite its benefits, many patients with AF do not receive warfarin therapy. One of the earliest studies examining the use of warfarin for AF was a retrospective case analysis of 95 AF patients.[33] The authors of this study concluded that the number of patients with AF who were prescribed warfarin was suboptimal. This conclusion was supported by subsequent studies that found that no more than 60% of patients with AF who were candidates for anticoagulant therapy received appropriate warfarin therapy.[34-37]

The underuse of warfarin results from a number of barriers. There is significant variability in how patients respond to warfarin, as well as multiple food and drug interactions. Hylek et al reported that patients were often discharged without a prescription for warfarin because of the presence of a contraindication such as an inability to tolerate therapy.[38] Physicians in this study were also hesitant to prescribe warfarin in older adults (80 and older) because of the risk of a fall or hemorrhage.[38] These results were supported by a study of 596 family physicians who did not prescribe warfarin for AF patients who had a history of nosebleeds, had received treatment for a peptic ulcer, or had a minor risk of falling.[39] There is also a belief among physicians that certain patients will either refuse treatment or be noncompliant to therapy.[40]

The difficulties associated with the administration of warfarin may also adversely affect its use. Warfarin has a slow onset and offset of action, which is helpful if a patient misses a dose but can be problematic if a patient needs to discontinue therapy quickly.[23] Monitoring for the narrow INR therapeutic range needed to balance the adequate prevention of anticoagulation with concomitant prevention of hemorrhage can also be difficult for both physicians and patients.[23] Even with strict laboratory monitoring, 1% to 3% of patients receiving warfarin still experience a hemorrhage.[23]

Physician experience with warfarin also affects its therapeutic use. Physicians are less likely to prescribe warfarin if their previous patients experienced a bleeding event following warfarin therapy.[39] On the other

Table 3. *Assessing bleeding risk in patients receiving warfarin.*[44,49]

Risk Scheme	Bleeding Risk		
	Low	Moderate	High
$HEMORR_2HAGES$	0–1	2–3	≥4
HAS-BLED	0	1–2	≥3

$HEMORR_2HAGES$[44]		HAS-BLED[49]	
• Hepatic or renal disease	• Hypertension uncontrolled	• Hypertension	• Labile INR (<60% of time in therapeutic range)
• Ethanol abuse	• Anemia	• Abnormal renal/liver function (1 point each)	• Elderly (>65 years)
• Malignancy	• Genetic factors	• Stroke	• Drug or alcohol use concomitantly (1 point each)
• Old age ≥75 years	• Excessive fall risk	• Bleeding history	
• Reduced platelet function	• Stroke		
• Rebleeding risk (2 points)			

- Table above indicates bleeding risk for each scheme
  - Scoring $HEMORR_2HAGES$: 1 point is added for each risk factor; 2 is added for a previous bleed (maximum 12 points)
  - Scoring HAS-BLED: 1 point for each risk factor, as indicated above (maximum 9 points)
- HAS-BLED more accurately predicted bleeding in both warfarin-naïve patients and those taking concurrent warfarin and aspirin than other bleeding risk tools[49]

hand, physicians who have a long history of using warfarin are more likely to prescribe the agent and less likely to be concerned with bleeding risks.[39]

Because the risk of bleeding is a major concern in patients who are candidates for warfarin therapy and their physicians, bleeding prediction models have been developed to determine which patients have the greatest risk of hemorrhage due to warfarin. Assessing bleeding risk prior to warfarin therapy is an important element of the 8th edition of the *Evidence-Based Clinical Practice Guidelines* from the American College of Chest Physicians (ACCP).[27] The ACCP guidelines state that the largest contributors to hemorrhage are intensity of the anticoagulant, patient characteristics (eg, age), concurrent use of medications that interfere with hemostasis, and length of therapy.[41] The bleeding risk–stratification tools that have been developed focus on patient-specific factors related to hemorrhage (Table 3).[44,49]

The major differences between the available bleeding risk–stratification tools primarily relate to which bleeding risk factors are included and how much they contribute to a final score.[42-45] Of the available risk-assessment tools, only the Outpatient Bleeding Risk Index (OBRI) has been validated independently. A bleeding risk score for the OBRI is based on summing the total number of bleeding risk factors. These include an age of 65 years or older, history of gastrointestinal bleeding or stroke, and one of the following: recent myocardial infarction, renal insufficiency, severe anemia at discharge, or diabetes mellitus.[42] In the initial validation study of 264 outpatients who were starting on warfarin for various indications (not just AF), the cumulative incidence of hemorrhage was 3% in the low-risk group, 12% in the intermediate-risk group, and 53% in the high-risk group. Additional validation studies confirmed the ability of OBRI to discriminate between patients with different levels of bleeding risk.[46,47]

Other bleeding risk assessment tools have been specifically studied in patients with AF. These include The $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older adults [>75 years], reduced platelet count or function, hypertension, anemia, genetic factors, excessive fall risk, and stroke) risk tool, which assigns 2 points for a prior bleed and 1 point for every risk factor contained in the $HEMORR_2HAGES$ acronym, and then totals these points.[44] $HEMORR_2HAGES$ has been reported to have greater predictive accuracy of bleeding among patients with AF than OBRI.[18]

One of the newest bleeding risk-assessment tools is referred to as HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [> 65 years], drugs/alcohol).[48] Results for this tool are calculated by assigning 1 point for every risk factor contained in the HAS-BLED acronym and determining the sum. A study using data from the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III and V trials found that HAS-BLED more accurately predicted bleeding in both warfarin-naïve patients and those taking concurrent warfarin and aspirin than the $HEMORR_2HAGES$ tool.[49]

Case Update 1

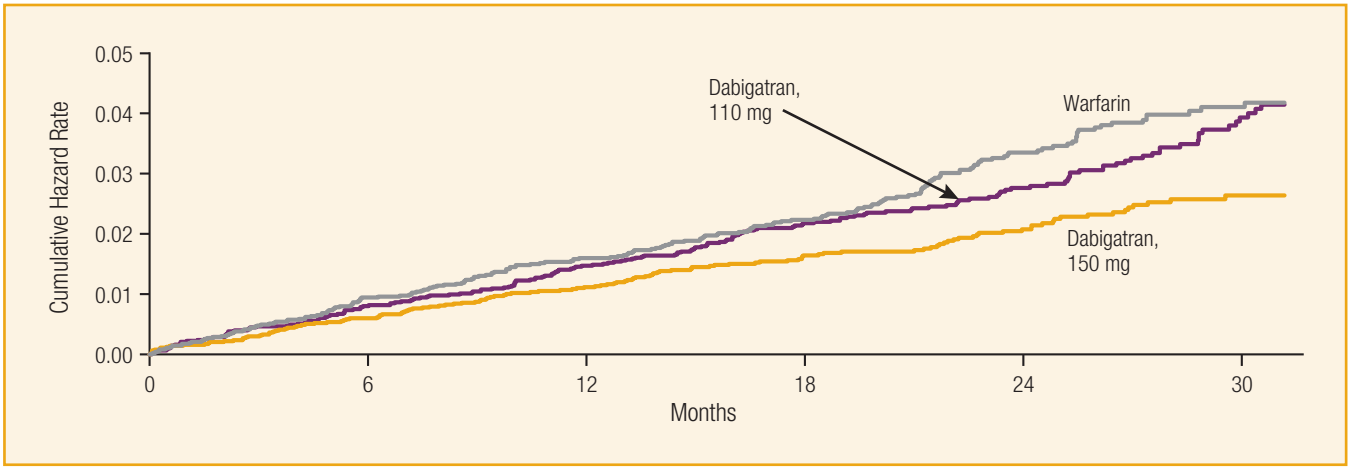
Two years later, the patient presents to an emergency room with intermittent left-sided facial and tongue numbness. His symptoms began 6 hours prior to presentation and occur intermittently. He denies any other neurological or cardiopulmonary symptoms. His medications include warfarin, glipizide, atorvastatin, and lisinopril. He has been taking warfarin for 2 years and his INR has often been out of the therapeutic range over the past year, despite frequent coagulation monitoring and dose adjustments. His physical examination, including a thorough neurological assessment, is unremarkable. His INR is 1.5 and his estimated creatinine clearance (CrCl) using the Cockcroft-Gault method is 55. Noncontrast computed tomography and magnetic resonance imaging of the brain show no acute abnormalities. Transient ischemic attack (TIA) is diagnosed based on the patient's clinical presentation. He is admitted for observation and is treated with 1 mg/kg enoxaparin every 12 hours. In part because of the patient's difficulty in achieving a consistently therapeutic INR, the decision is made to try an alternative anticoagulant. Dabigatran is initiated in place of warfarin.

Anticoagulant Therapy: Newly Approved Treatment Options

The difficulties associated with the use of warfarin (outlined in previous sections) have prompted the development of alternative anticoagulants. Recently, two new drugs have been approved by the Food and Drug Administration (FDA) for the prevention of stroke in patients with AF: dabigatran and rivaroxaban. Dabigatran, a direct thrombin inhibitor, functions by preventing the conversion of fibrinogen to fibrin, preventing platelet activation, and interrupting the positive-feedback loop in which thrombin maintains thrombus formation through activation of factors V, VIII, and XI.[50,51] The approval of dabigatran was based on results from the phase 3 RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial.[52] Dabigatran was found to be noninferior to warfarin in regard to the prevention of thromboembolism, but without the complication of maintaining a strict therapeutic range and with lower bleeding risk.

The RE-LY trial was a prospective, blinded, noninferiority trial of 18,113 patients with AF who were randomly assigned to one of three treatment groups (110 mg of dabigatran twice a day, 150 mg of dabigatran twice a day, or dose-adjusted warfarin) and followed for 2 years.[52] Among those who received warfarin, the target INR range was maintained 64% of the time. The FDA-approved 150 mg BID dose of dabigatran had lower rates of stroke or systemic embolism than did warfarin (Figure 1; relative risk 0.66; 95% CI, 0.53 to 0.82; $P<0.001$).[52] The rate per year of major bleeding was 3.36% in the warfarin group and 3.11% in the 150 mg dabigatran group (relative risk, 0.93; 95% CI, 0.81–1.07; $P=0.31$ vs warfarin).

Figure 1. *Cumulative hazard rates for the occurrence of stroke or systemic embolism in patients receiving warfarin, dabigatran 110 mg, or dabigatran 150 mg.*[52]



In February 2011, an addendum to the 2011 ACCF/AHA/HRS AF guidelines for the inclusion of dabigatran was published.[53] In its recommendations, the guideline committee noted that dabigatran can be used as an alternative to warfarin for the prevention of stroke or thromboembolism in patients with paroxysmal or permanent AF who are at risk of stroke or systemic embolism. The prophylactic use of dabigatran is not recommended in patients with a prosthetic heart valve, hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min), or advanced liver disease. Before a patient on warfarin therapy can be switched to dabigatran, his or her INR value should be below 2.0.[54] The procedure for switching from dabigatran to warfarin is more complex and based on kidney function (Table 4).[54] Because of the risk of hemorrhage with dabigatran therapy, a preliminary algorithm has been developed to help guide the management of bleeding events (Figure 2).[55]

Case Update 2

The patient is evaluated 2 weeks after discharge. He no longer has any neurological symptoms; however, he is now experiencing midepigastric abdominal pain and reflux, which began several days after initiating dabigatran. The patient's abdominal symptoms subside once he starts taking his dabigatran with meals.

Table 4. *How to switch a patient from dabigatran to warfarin based on kidney function.*[54]

Creatinine Clearance (mL/min)	Days of Concurrent Treatment Before Dabigatran Discontinuation
>50	3
31–50	2
15–30	1
>15	N/A

Figure 2. *Preliminary algorithm for the management of bleeding in patients receiving dabigatran.*[55]

van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103:1124.

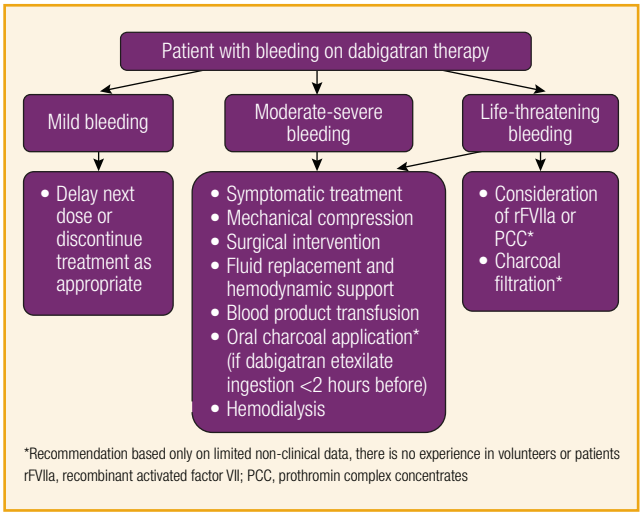


Table 5. *Rivaroxaban versus warfarin: primary end point of stroke or systemic embolism.*[58]

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	*P* Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6,958	188	1.7	7,004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7,061	189	1.7	7,082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7,081	269	2.1	7,090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

Although total bleeding and life-threatening bleeding were reduced, patients in the RE-LY trial who received 150 mg of dabigatran had a higher risk of gastrointestinal bleeding than did patients who received warfarin.[52, 56] Dyspepsia was the only adverse event that occurred more frequently in patients who received dabigatran than warfarin ($P<0.001$ for both dabigatran doses relative to warfarin). In addition, patient discontinuation of therapy was significantly higher with dabigatran at either dose than with warfarin.[52] After the first year of treatment, 15% and 16% of patients who received dabigatran at the 110-mg or 150-mg dose, respectively, discontinued therapy compared with 10% of the patients taking warfarin; after the second year of treatment, 21% of patients who received either dose of dabigatran discontinued compared with 17% of those who received warfarin ($P<0.001$ for both first and second year discontinuation).[52]

Several subgroup analyses of the RE-LY trial data have been published. One analysis found that patients with a prior stroke or TIA had the same relative effects against stroke or systemic embolism as patients who had not had a stroke prior to trial enrollment.[56] Another subgroup analysis looked at the effect of exposure to vitamin K antagonists prior to enrollment in the RE-LY trial.[57] The 150-mg dose of dabigatran was more effective at reducing the occurrence of stroke and systemic embolism than was warfarin regardless of previous experience with a vitamin K antagonist. Episodes of major bleeding were similar for all treatment groups in vitamin K–naïve patients, whereas the rates of major bleeding for vitamin K–experienced patients did not differ between warfarin and dabigatran 150 mg.

In November 2011, rivaroxaban was approved for the prevention of stroke in patients with AF. It is a direct factor Xa inhibitor, preventing clot formation by blocking the conversion of prothrombin to thrombin via a formation of prothrombinase complex involving factor V.[50] In contrast to indirect factor Xa inhibitors such as fondaparinux, direct factor Xa inhibitors are able to inhibit both free factor Xa and factor Xa that is part of the prothrombinase complex.[50] Rivaroxaban was examined in a phase 3 clinical trial called ROCKET-AF (Rivaroxaban-Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[58] In this study, 14,264 patients with nonvalvular AF who either had a history of stroke or had two or more clinical risk factors for stroke were randomly assigned to receive either rivaroxaban (20 mg once a day) or dose-adjusted warfarin in a double-blind, double-dummy noninferiority trial.[58] In the primary analysis, the primary end point (either stroke or systemic embolism) occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio [HR] in the rivaroxaban group, 0.79; 95% CI, 0.66 to 0.96; $P<0.001$ for noninferiority; Table 5).[58] In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year; HR, 0.88; 95% CI, 0.74 to 1.03; $P<0.001$ for noninferiority; $P=0.12$ for superiority).[58] Major and nonmajor clinically relevant bleeding occurred in 1,475 patients in the rivaroxaban group (14.9% per year) and in 1,449 in the warfarin group (14.5% per year) (HR, 1.03; 95% CI, 0.96 to 1.11; $P=0.44$), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, $P=0.02$) and fatal bleeding (0.2% vs. 0.5%, $P=0.003$) in the rivaroxaban group.[58] The authors concluded that rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, and that there was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.[58]

Case Update 3

Six months later, the patient presents for a preoperative evaluation prior to a right-knee replacement to treat osteoarthritis. His CrCl is 55 mL/min, so he is ordered to stop taking dabigatran 2 days prior to surgery. After uneventful surgery, the patient was instructed to take a prophylactic dose of enoxaparin for 2 days beginning on postoperative day 1. On postoperative day 3, he restarted dabigatran. Approximately 24 hours later, he experienced increasing pain and swelling of his surgically repaired knee. He was evaluated in the emergency department and found to have hemarthrosis. He received a preoperative evaluation prior to a planned surgical prodecure to treat the surgical-site bleeding.

Anticoagulant Therapy: Agents in Development

The approval of dabigatran and rivaroxaban marks the first time in decades that an anticoagulant has been approved for the prevention of stroke in patients with AF. Despite the data showing efficacy in preventing stroke or embolism, the risk of hemorrhage is still a concern with the approved 150-mg dose of dabigatran and 20-mg dose of rivaroxaban. Therefore, anticoagulants currently in development target not only the prevention of stroke and embolism but also a significant reduction in the risk of hemorrhage compared with warfarin.

Table 6. *Comparison of pharmacokinetic profiles of available and investigational anticoagulants.*[50,51,59]

Agent	Target	Prodrug	Dosing	Oral Bioavailability	Monitoring	Half-Life	Metabolism and Elimination	Time to Peak Plasma	Drug Interactions
Warfarin	Vitamin K epoxide	No	Once daily	>95%	INR-adjusted	40 hrs	CYP 2C9, 3A4, 1A2	72–96 hrs	CYP 2C9, 1A2, and 3A4
Dabigatran	Thrombin	Yes	Fixed, once or twice daily	6.5%	None	14–17 hrs	80% renal, 20% fecal	2 hrs	Potent P-glycoprotein inhibitor, rifampicin, quinidine, amiodarone, dronedarone, ketoconazole, verapamil
Rivaroxaban	Factor Xa	No	Fixed, once or twice daily	80%	None	5–9 hrs in younger patients; 9–13 hrs in older adults	CYP3A4; 66% renal, 33% fecal	2.5–4 hrs	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors
Apixaban	Factor Xa	No	Fixed, twice daily	~66%	None	8–15 hrs	CYP3A4; 75% fecal, 25% renal	3 hrs	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors
Edoxaban	Factor Xa	No	Fixed, once daily	50%	None	9–11 hrs	CYP3A4; 65% fecal, 35% renal	1–2 hrs	Potent CYP3A4 inhibitors and P-glycoprotein inhibitors

Among the current classes of investigational agents being developed, the factor Xa inhibitors are among the furthest along in clinical development (Table 6).[50,57,59]

Currently, there are two additional factor Xa inhibitors being studied for stroke prevention in patients with AF: apixaban and edoxaban. A recent study comparing apixaban with warfarin reported the results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[60] In this randomized, double-blind trial, apixaban 5 mg twice daily was compared with warfarin (target INR, 2.0 to 3.0) in 18,201 patients with AF and at least one additional risk factor for stroke; the median duration of follow-up was 1.8 years. The rate of the primary outcome (ischemic or hemorrhagic stroke or systemic embolism) was 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group (HR with apixaban, 0.79; 95% CI, 0.66 to 0.95; $P<0.001$ for noninferiority; $P=0.01$ for superiority).[60] The rate of major bleeding was 2.13% per year in the apixaban group compared with 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60 to 0.80; $P<0.001$), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR, 0.89; 95% CI, 0.80 to 0.99; $P=0.047$).[60] The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (HR, 0.51; 95% CI, 0.35 to 0.75; $P<0.001$), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74 to 1.13; $P=0.42$).[60] The authors concluded that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.[60]

A 12-week randomized double-blind phase 2 trial of edoxaban was designed to examine the safety of different doses of the agent (30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid) versus dose-adjusted warfarin in 1,146 patients with AF who were at risk of stroke.[61] Because of excess bleeding in 180 patients, the edoxaban 60 mg BID group was terminated early. The incidence of major and clinically relevant nonmajor bleeding events was similar between warfarin and the edoxaban 30 mg QD and edoxaban 60 mg QD groups, whereas the edoxaban 30 mg BID and edoxaban 60 mg BID groups had higher rates of major and clinically relevant minor bleeding events than warfarin. Overall, the fraction of

patients with serious treatment-related adverse events was similar between those who received edoxaban and those who received warfarin. Based on these phase 2 data, a phase 3 study, ENGAGE AF-TIMI 48 (Effective anticoagulation with factor xA next Generation on Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48) is currently under way. This randomized, double-blind, double-dummy noninferiority trial will compare the effects of two doses of edoxaban (30 mg per day or 60 mg per day) against dose-adjusted warfarin in patients with AF.[62] The primary end point will be to determine if edoxaban is noninferior to warfarin for stroke and embolism.

Summary

AF is a condition that increases in frequency as a person ages and is a known risk factor for the development of stroke. In a person suspected of having AF, a definitive diagnosis requires the use of an ECG to identify the trademark rapid oscillations that replace the standard P wave. Once AF is diagnosed, it is important to determine whether the patient has a medical condition that is causing it.

Management of AF consists not only of therapies designed to reverse the arrhythmia but also therapies to prevent stroke with anticoagulants. The most common anticoagulants used for the prevention of stroke in patients with AF are aspirin and warfarin. Aspirin is reserved for patients with a low risk of stroke, whereas warfarin is used in patients with a moderate to high risk of stroke. Despite being superior to aspirin in preventing stroke, warfarin is difficult to use and carries a significant risk of hemorrhage. Dabigatran has recently been approved for stroke prevention in patients with AF and has been shown to have benefit in reducing stroke or embolism; however, bleeding is still a concern. Several factor Xa inhibitors are currently being investigated for their ability to prevent stroke and reduce the risk of bleeding and hemorrhage compared with warfarin.

Log on to http://jeffline.jefferson.edu/jeffcme/AFIBSTR to complete the posttest and the activity evaluation form.

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Posttest

1. **The 1-year mortality rate of atrial fibrillation (AF) associated with stroke is**
   a. 10%
   b. 20%
   c. 30%
   d. 50%
   e. 60%

2. **Which of the following is NOT a risk factor for stroke associated with AF?**
   a. Age
   b. Autoimmune disease (eg, lupus)
   c. Congestive heart failure
   d. Diabetes mellitus
   e. Hypertension

3. **Your patient, age 66, was previously diagnosed with AF and diabetes; she is normotensive. She reports to your office with symptoms of a transient ischemic attack (TIA). What is her $CHADS_2$ risk score?**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

4. **Prior to this patient's reported symptoms of possible TIAs, she was prescribed aspirin 81 mg daily. Was her anticoagulant therapy prescribed according to current ACCF/AHA/HRS guidelines?**
   a. Yes, aspirin alone was recommended in the guidelines
   b. No, she should have been taking aspirin 325 mg/day
   c. No, she should have been taking aspirin plus clopidogrel
   d. No, she should have been taking warfarin or dabigatran
   e. No, she should have been taking aspirin plus warfarin

5. **After confirming that this patient had a TIA, you now prescribe warfarin. According to ACCF/AHA/HRS guidelines, what is the target international normalized ratio (INR) range**
   a. 1.0–1.5
   b. 1.6–2.5
   c. 2.0–3.0
   d. 2.5–3.5
   e. This patient has a high risk of bleeding and should not be given warfarin

6. **Which of the following statements regarding warfarin is TRUE?**
   a. It has been reported that patients taking warfarin have a relative risk reduction for stroke of 36% compared with aspirin
   b. The slow offset of warfarin action is problematic if a patient forgets to take a dose
   c. It is recommended that the INR should be measured less frequently than the usual 4-week interval when virtually any drug, dietary supplement, or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin
   d. Even with strict laboratory monitoring and maintenance of therapeutic INR, 3% to 6% of patients receiving warfarin still experience a hemorrhage
   e. Inability to maintain a therapeutic INR range at least 90% of the time has been associated with a greater incidence of thromboembolic events, including stroke

7. **Which of the following is considered a risk factor for bleeding in patients with AF who are prescribed warfarin?**
   a. Hypertension
   b. Obesity
   c. Smoking
   d. Family history of autoimmune disease
   e. Glaucoma

8. **Which of the following statements regarding dabigatran is TRUE?**
   a. The ACCF/AHA/HRS has not recommended dabigatran for use in patients with AF
   b. The bleeding risk for dabigatran 150 mg was not significantly different from that associated with warfarin in AF patients
   c. Patients receiving dabigatran do not need to be monitored for therapeutic range of the drug
   d. Dabigatran is not as effective in preventing clots in patients who have already received vitamin K antagonists as it is in patients who are vitamin K–naïve
   e. Hemorrhage is not a major medical concern in patients using dabigatran

9. **Which of the following statements regarding rivaroxaban is TRUE?**
   a. Rivaroxaban is a direct thrombin inhibitor
   b. Rivaroxaban was found to be superior to dabigatran for prevention of stoke or systemic embolism
   c. Rivaroxaban was found to be noninferior to warfarin for prevention of stroke or systemic embolism
   d. Major and nonmajor clinically relevant bleeding was significantly greater with warfarin than with rivaroxaban
   e. Major and nonmajor clinically relevant bleeding was significantly greater with dabigatran than with rivaroxaban

10. **Which of the following agent(s) in development has/have been reported in phase III trials to be superior to warfarin for anticoagulation efficacy in patients with AF?**
    a. Apixaban
    b. Edoxaban
    c. Fondaparinux
    d. None were noninferior or superior to warfarin for both anticoagulation and bleeding risk in phase III trials
    e. Both apixaban and edoxaban

Reducing Stroke Risk in Patients With Atrial Fibrillation

Release date: December 2011 • **Expiration date:** December 31, 2012

Please refer to the Method of Participation section in the front of this monograph for additional information.
Complete this activity and request credits online at: ***http://jeffline.jefferson.edu/jeffcme/AFIBSTR*** *(or you may complete and submit the form below).*

PARTICIPANT INFORMATION

PLEASE PRINT CLEARLY. Complete all items to receive credit for this program.

E-mail (required to receive CME certificate) _____

Specialty (please check one):

◯ FP ◯ GP ◯ IM ◯ Cardiology ◯ Other _____

Medical profession (please check one):

◯ Physician ◯ NP ◯ PA ◯ Nurse ◯ RN ◯ Other _____

Last Name _____ First Name _____ MI _____

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City _____ State _____ ZIP _____

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POSTTEST ANSWER SHEET

Circle only one answer per question.

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ	6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ	7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ	8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ	9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ	10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	Ⓔ

EVALUATION

Rate the extent to which	**Very High**	**High**	**Moderate**	**Low**	**Very Low**
1. Overall objectives of this activity were met	⑤	④	③	②	①
2. Individual objectives of this activity were met					
a. Review current guidelines for the management of AF	⑤	④	③	②	①
b. Apply risk-assessment strategies when managing patients with AF	⑤	④	③	②	①
c. Optimize clinical management plans for the prevention of stroke in patients with AF that utilize risk-benefit assessments of current and emerging anticoagulant therapies	⑤	④	③	②	①
3. You were satisfied with the overall quality of this activity	⑤	④	③	②	①
4. Content was relevant to your practice	⑤	④	③	②	①
5. Participation in this activity changed your knowledge/attitudes	⑤	④	③	②	①
6. You will make a change in your practice as a result of participation in this activity	⑤	④	③	②	①
7. The activity presented scientifically rigorous, unbiased, and balanced information	⑤	④	③	②	①
8. Content was free of commercial bias	⑤	④	③	②	①

If you believe the content exhibited commercial bias, please describe the specifics. _____

_____

PERFORMANCE SELF-REFLECTION

1. How many patients with atrial fibrillation do you typically see in a week?

○ 0 ○ 1–5 ○ 6–10 ○ 11–15 ○ 16–20 ○ 21–25 ○ >25 ○ I do not see patients.

2. How many years have you been in practice?

○ 0–5 ○ 6–10 ○ 11–15 ○ 16–20 ○ 21–25 ○ >25

Please indicate, on the left side, how often you currently use each of the listed strategies with respect to the treatment of patients with joint pain and swelling. Then, on the right side, indicate how often you *now plan* to use these same strategies based on your participation in this CME activity:

Your Current Use						Your Planned Use				
Always	Often	Some-times	Not Often	Never	Clinical Practice Strategies	Always	Often	Some-times	Not Often	Never
⑤	④	③	②	①	a. Use a risk stratification scheme to help determine appropriate anticoagulant therapy for patients with AF	⑤	④	③	②	①
⑤	④	③	②	①	b. Determine bleeding risk for AF patients to help determine appropriate anticoagulant therapy	⑤	④	③	②	①
⑤	④	③	②	①	c. Maintain appropriate INR targets for AF patients taking warfarin	⑤	④	③	②	①
⑤	④	③	②	①	d. Use appropriate procedures when switching between warfarin and dabigatran or dabigatran and warfarin	⑤	④	③	②	①

Which ONE of the following best describes the impact of this activity on your performance

○ This program will not change my behavior because my current practice is consistent with what was taught

○ This activity will not change my behavior because I do not agree with the information presented

○ I need more information before I can change my practice behavior

○ I will immediately implement the information into my practice

- **How are you going to change your practice?** _____

_____

- **What information remains unclear?** _____

_____

- **Questions or comments regarding this activity** _____

_____

○ I would like to receive information about future educational activities on the topic of AF.

PARTICIPANT STATEMENT FOR CERTIFICATION:

Time needed to complete this activity: ○ 0.5 h ○ 0.75 h ○ 1.0 h

I hereby state that I have completed this activity independently.

Signature _____ Date _____

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