New Options for Stroke Prevention in Atrial Fibrillation

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Abstract

Randomized trials have demonstrated that warfarin is effective for stroke prevention in patients with atrial fibrillation (AF), yielding relative risk reductions for ischemic stroke of nearly 70%. However, successful use of warfarin requires frequent monitoring and dose adjustment to maintain an international normalized ratio (INR) within the range of 2.0 to 3.0. Many clinicians and patients have been reluctant to use warfarin therapy in AF, with underuse generally attributed to the inconvenience of INR monitoring, complexities of drug and dietary interactions associated with warfarin, and perceived bleeding risk. The ensuing search for safe, effective alternatives with a lower associated risk of bleeding and no need for monitoring and dose adjustment has focused attention on more specific inhibitors of the clotting cascade, such as factor Xa inhibitors or direct thrombin inhibitors. The direct thrombin inhibitor dabigatran has recently been approved by the US Food and Drug Administration for the prevention of stroke in patients with AF. New factor Xa inhibitors apixaban, rivaroxaban, and edoxaban are also currently being studied in stroke prevention trials in patients with AF to determine their comparability with warfarin. It is anticipated that fixed-dose administration of these new oral agents will provide effective anticoagulation without the need for frequent monitoring and with a lower risk of bleeding events.

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For author information and disclosures, see end of text.

Historically, the options primarily recommended for antithrombotic therapy in patients with atrial fibrillation (AF) have been aspirin and warfarin, a vitamin K antagonist.[1] In 5 prospective, randomized, controlled clinical trials conducted in patients with nonrheumatic AF, warfarin was shown to significantly reduce the risk of thromboembolism by 48% to 72%.[2] However, warfarin also has complex pharmacokinetics and pharmacodynamics, including interactions with many medications and foods.[3] Moreover, the use of warfarin is complicated by a narrow therapeutic window and a need for continual laboratory monitoring to avoid both the risk of major bleeding events and the risk of inadequate anticoagulation. Aspirin, although somewhat effective in preventing stroke in AF, is inferior to warfarin and is primarily used in low-risk patients.[1] These issues, as well as the risks associated with patient nonadherence, have spurred efforts to improve the safety, efficacy, and convenience of anticoagulation therapy by targeting specific steps in the coagulation cascade, thus reducing the number of potential unwanted drug effects.[3,4]

Any anticoagulant, like unfractionated heparin, low molecular weight heparins (LMWH), and warfarin, affects multiple components of the coagulation cascade. Vitamin K antagonists, including warfarin, disrupt the production of multiple functional vitamin K–dependent clotting factors (II, VII, IX, and X), as well as the anticoagulant proteins C and S (Figure 1).[3] Argatroban, lepirudin, and bivalirudin are direct thrombin inhibitors that do not require thrombin for their anticoagulant effect. Newer agents have been developed that directly target and inhibit specific coagulation proteins.

Direct thrombin inhibitors (eg, argatroban, lepirudin, bivalirudin), LMWHs, and the factor Xa inhibitor fondaparinux overcome some of the disadvantages of unfractionated heparin, but require intravenous or subcutaneous administration, are contraindicated or difficult to use in patients with hepatic or renal dysfunction, and have not proved useful for long-term antithrombotic prophylaxis in patients with AF.[3] For example, in a study of long-term anticoagulation in patients with AF that compared the once-weekly LMWH idraparinux and warfarin, idraparinux was associated with a significantly higher risk of bleeding.[5] New oral agents could be used in a variety of settings, and some are currently in clinical trials to investigate their efficacy in AF and the possible advantages over current choices.[6-9] It is anticipated that these new agents will eventually

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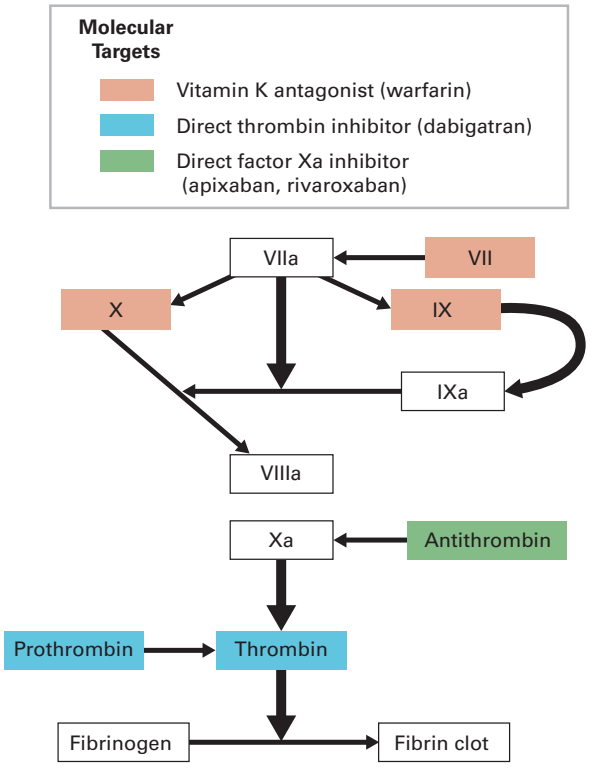
■ **Figure 1.** Oral Antithrombotic Agents Used for the Treatment of Atrial Fibrillation Act on Different Molecular Targets in the Coagulation Cascade[3]



Warfarin affects clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. Direct thrombin inhibitors act directly and specifically on thrombin activity, whereas factor Xa inhibitors specifically target factor Xa in the coagulation cascade.
Adapted from Trujillo TC. *Am J Health Syst Pharm.* 2010;67(suppl 6):S17-S25.

replace warfarin in prophylactic and therapeutic regimens in many patients, including those with AF.

Direct Thrombin Inhibitors: Dabigatran

The efficacy of dabigatran and warfarin (adjusted to an international normalized ratio [INR] of 2.0-3.0 according to monthly measurements) in stroke prevention has been assessed in high-risk patients with AF. The stable pharmacodynamics and pharmacokinetics of dabigatran permitted fixed dosing (110 mg or 150 mg twice daily) with no need for monitoring.[10,11] In addition to AF, these high-risk subjects also had at least 1 of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. This study excluded patients who have a severe heart valve disorder, had a stroke within 14 days or a severe stroke within 6 months before screening, have conditions known to raise the risk of hemorrhage, have a creatinine clearance less than 30 mL/min, have active liver disease, or are pregnant.

Over a median follow-up period of 2 years, the study followed 18,113 patients for incidence of primary (ie, stroke or systemic embolism) or secondary (ie, stroke, systemic embolism, or death) outcome.[10,11] The primary safety outcome was major hemorrhage. This noninferiority trial made an open-label comparison between warfarin and dabigatran 110 mg or 150 mg twice daily. The 2 dabigatran regimens were assigned in a blinded fashion. In comparison with warfarin, both dabigatran regimens met noninferiority criteria in their primary outcomes, and the higher dose of dabigatran was superior in efficacy to warfarin, as summarized in **Table 1**. The individual rates of stroke and systemic embolism were 1.69% per year for warfarin; 1.53% per year for dabigatran 110 mg, with a relative risk (RR) of 0.91 (95% confidence interval [CI], 0.74-1.11; P <.001 vs warfarin); and 1.11% per year for dabigatran 150 mg with an RR of 0.66 (95% CI, 0.53-0.82; P <.001) (Table 1 and **Figure 2**).

The incidence of major bleeding was 3.36% per year in the warfarin group, 2.71% per year for the dabigatran 110-mg regimen (RR = 0.80; 95% CI, 0.69-0.93; P = .003 vs warfarin), and 3.11% per year for the dabigatran 150-mg regimen (RR = 0.93; 95% CI, 0.81-1.07; P = .31).[10] Rates of hemorrhagic stroke were 0.38% per year with warfarin, 0.12% per year with dabigatran 110 mg (P <.001 vs warfarin), and 0.10% per year with dabigatran 150 mg (P <.001) (Table 1 and **Figure 3**). By selectively inhibiting only thrombin, dabigatran may block clot formation with a greater specificity than warfarin and it does not affect other aspects of the coagulation cascade, thus potentially mitigating the risk of bleeding. Alternatively, a lower degree of variability in the anticoagulant effect of dabigatran may underlie its association with a reduced risk of bleeding. Life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (P <.05 for all comparisons of dabigatran with warfarin) (Table 1 and Figure 3). Major gastrointestinal bleeding was significantly higher with dabigatran 150 mg than warfarin.

The length of time spent within the optimal therapeutic range for warfarin (ie, INR of 2.0-3.0) determines its efficacy and safety, and is a gauge of the quality of the warfarin regimen. To reveal whether the quality of warfarin therapy played a role in the results of the Randomized Evaluation of

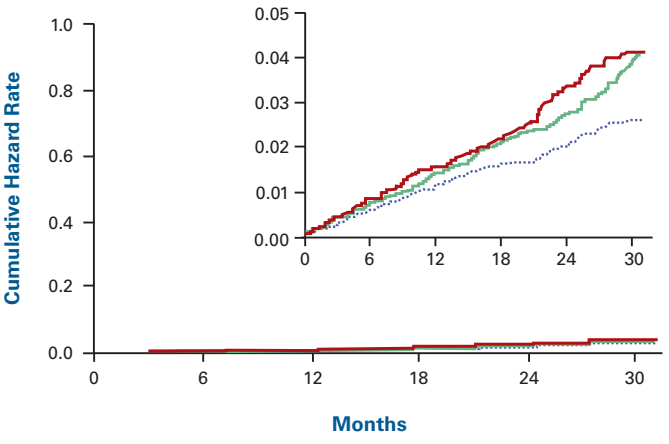
Table 1. RE-LY Outcomes, Stroke, and Bleeding Events in Patients With Atrial Fibrillation[10]

	Dabigatran 110 mg Daily vs Warfarin[a]			Dabigatran 150 mg Daily vs Warfarin[a]		
Outcome	**RR**	**95% CI**	***P*[a]**	**RR**	**95% CI**	***P*[a]**
Stroke or Systemic Embolism	0.91	0.74-1.11	.34[b]	0.66	0.53-0.82	<.001[b]
Stroke	0.92	0.74-1.13	.41	0.64	0.51-0.81	<.001
Hemorrhagic	0.31	0.17-0.56	<.001	0.26	0.14-0.49	<.001
Ischemic or Unspecified	1.11	0.89-1.4	.35	0.76	0.60-0.98	.03
Nondisabling Stroke	0.86	0.61-1.22	.40	0.62	0.43-0.91	.01
Disabling or Fatal Stroke	0.94	0.73-1.22	.65	0.66	0.50-0.88	.005
Bleeding Events						
Major Bleeding	0.80	0.69-0.93	.003	0.93	0.81-1.07	.31
Gastrointestinal Bleeding[c]	1.10	0.86-1.41	.43	1.50	1.19-1.89	<.001
Minor Bleeding	0.79	0.74-0.84	<.001	0.91	0.85-0.97	.005
Life-Threatening Bleeding	0.68	0.55-0.83	<.001	0.81	0.66-0.99	.04
Intracranial Bleeding	0.31	0.20-0.47	<.001	0.40	0.27-0.60	<.001

CI indicates confidence interval; RE-LY, Randomized Evaluation of Long-term anticoagulation Therapy; RR, relative risk.
[a]Dose-adjusted warfarin, international normalized ratio 2.0-3.0.
[b]Respective *P* values for noninferiority were *P* <.001 (dabigatran 110 mg) and *P* <.001 (dabigatran 150 mg).
[c]Gastrointestinal bleeding could be life threatening or non–life threatening.
Adapted from Connolly SJ, Ezekowitz MD, Yusuf S, et al. *N Engl J Med.* 2009;361:1139-1151.

Long-term anticoagulation Therapy (RE-LY) study, a post hoc analysis compared primary and secondary outcomes for both dabigatran regimens with respective warfarin outcomes, relative to the time patients given warfarin spent within the therapeutic range (TTR).[11] Regression analysis revealed no significant interactions between TTR and prevention of the primary outcome (ie, stroke or systemic embolism) for either dabigatran regimen. The *P* values for interaction were *P* = .89 (dabigatran 110 mg) and *P* = .20 (dabigatran 150 mg) versus warfarin. There were reductions in the rates of stroke and intracranial bleeding with dabigatran 150 mg and similar reductions in stroke and major and intracranial bleeding with dabigatran 110 mg, irrespective of INR control. The benefits of dabigatran 150 mg in reducing stroke, dabigatran 110 mg in reducing bleeding, and both regimens in reducing intracranial bleeding compared with warfarin were shown to be consistent regardless of the quality of INR at individual study centers.

Figure 2. Primary Outcome in Patients With Atrial Fibrillation at High Risk of Stroke[10]



Rates of stroke and systemic embolism for warfarin therapy (red solid line) versus dabigatran 110 mg twice daily (blue solid line) or 150 mg twice daily (blue dotted line). Warfarin versus dabigatran 110 mg: relative risk (RR) = 0.91 (95% confidence interval [CI], 0.74-1.11; *P* <.001); 150 mg: RR = 0.66 (95% CI, 0.53-0.82; *P* <.001).
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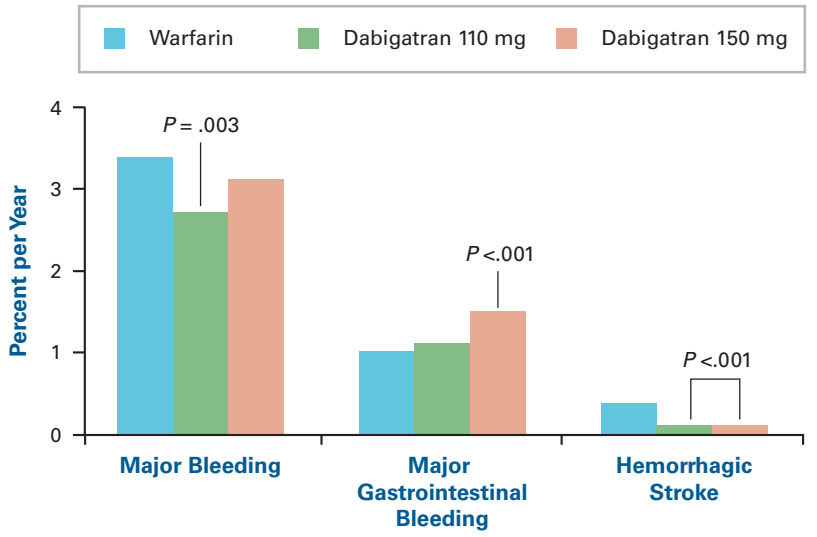
Factor Xa Inhibitors

Recent results from the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial that compared apixaban, a novel selective direct factor Xa inhibitor, with aspirin for primary stroke prevention in AF, have been published.[6] The trial was stopped early after a first analysis showed a clear advantage with apixaban. Subjects who had AF and 1 or more risk factors for stroke were interviewed to identify any factors that would make them unsuitable

Figure 3. Bleeding Events With Dabigatran Versus Warfarin (International Normalized Ratio 2.0-3.0)[10]



Dabigatran 110-mg regimen: relative risk (RR) for major bleeding = 0.80 (95% confidence interval [CI], 0.69-0.93; $P = .003$). Dabigatran 150-mg regimen: RR = 0.93 (95% CI, 0.81-1.07; $P = .31$). Adapted from Connolly SJ, Ezekowitz MD, Yusuf S, et al. *N Engl J Med.* 2009;361:1139-1151.

for warfarin therapy, such as alcoholism, a history of canceling healthcare visits, an unwillingness to participate in consistent INR testing, and potential for drug interactions.[7] Because aspirin (81-324 mg daily) is the usual care for patients who are not good candidates for warfarin therapy, the patients received aspirin or apixaban (5 mg twice daily).

After a median follow-up of 1 year, the primary endpoints (ie, stroke or systemic embolic event) were 1.6% in the apixaban group versus 3.6% in the aspirin group, a reduction of more than 50% by apixaban relative to aspirin.[6] Relative risk reductions for the primary endpoint and various others are shown in Table 2. There was a significant increase in minor bleeding with apixaban (5.2% vs 4.1%; $P = .04$), but these events generally did not require intervention or result in discontinuation. Apixaban was well tolerated, as evidenced by the absence of liver toxicity.

Rivaroxaban is another factor Xa inhibitor that is currently under investigation in moderate-to-high–risk patients with AF; the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study will determine the efficacy and safety of rivaroxaban compared with warfarin for the prevention of thromboembolism.[8] During studies of venous thromboembolism prevention in orthopedic surgery patients, rivaroxaban demonstrated no food-drug interactions, and it has shown little tendency toward drug-drug interactions, including interactions with digoxin, aspirin, or nonsteroidal anti-inflammatory drugs, suggesting little need for monitoring with this agent.[12,13]

The selective, direct factor Xa inhibitor edoxaban is also currently being studied in comparison with warfarin for the prevention of stroke and systemic embolism in AF patients. The Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation – Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF–TIMI 48) is a large, phase 3, randomized, double-blind, double-dummy, multinational, noninferiority trial being conducted in patients with electrical documentation of AF lasting less than 12 months and a $CHADS_2$ (congestive heart failure, hypertension, age at least 75 years, diabetes mellitus, stroke) score of at least 2.[9] The safety of 4 fixed-dose regimens of edoxaban was previously compared with dose-adjusted warfarin therapy (INR 2.0-3.0) in patients with nonvalvular AF over a 3-month period.[14] At the end of that study, the safety profiles of edoxaban 30 mg and 60 mg once daily were similar to warfarin. Major plus clinically relevant bleeding occurred in 3.2% of patients randomized to warfarin, 3.8% of patients using edoxaban 60 mg once daily, and 3.0% of patients using edoxaban 30 mg once daily. There were no significant differences in hepatic enzyme elevations or bilirubin values among the groups.

Warfarin Therapy Versus New and Emerging Agents: Role of INR Control

It is anticipated that the low bleeding risk associated with dabigatran and emerging factor Xa inhibitors will bring greater attention to the role of consistency in INR monitoring and dose adjustment for patients with AF currently using warfarin. Consistency in maintaining an INR between 2.0 and 3.0 will be a key consideration in determining whether a patient with AF may benefit from using a newer agent with a lower bleeding risk. The post hoc analysis mentioned above that examined INR control at individual RE-LY study sites found that dabigatran 150 mg was associated with significantly fewer major bleeding events than warfarin at the study sites having the poorest INR control. At study sites having better INR control, the

Table 2. AVERROES Outcomes: Stroke and Bleeding Events in Patients With Atrial Fibrillation[6]

Outcome	Apixaban Versus Aspirin[a]		
	RR	95% CI	*P*
Stroke or Systemic Embolic Event (SEE)	0.46	0.33-0.64	<.001
Stroke	0.48	0.34-0.68	<.001
Ischemic	0.38	0.26-0.56	<.001
Hemorrhagic	1.01	0.38-2.68	.99
Type Not Determined	1.99	0.60-6.62	.26
SEE	0.15	0.03-0.69	.01
Bleeding Events			
Major Bleeding	1.14	0.74-1.75	.56
Clinically Relevant, Nonmajor Bleeding	1.18	0.88-1.58	.28
Minor Bleeding	1.27	1.01-1.61	.04
Fatal Bleeding Event	0.84	0.26-2.75	.77
Intracranial Bleeding	1.09	0.50-2.39	.83

AVERROES indicates Apixaban versus Acetylsalicylic Acid to Prevent Strokes; CI, confidence interval; RR, relative risk.
[a]Apixaban 5 mg twice daily; aspirin 81-324 mg daily.
Adapted from Connolly S. European Society of Cardiology 2010; August 28-September 1, 2010; Stockholm, Sweden.

incidence of major bleeding events was similar between dabigatran 150 mg and warfarin.[11] The rates of major bleeding associated with dabigatran 110 mg were significantly lower than those with warfarin, irrespective of TTR. In contrast to the primary and secondary outcomes of the study, examination of other outcomes including cardiovascular events and total mortality revealed significant interactions with the TTR. For vascular events, hemorrhagic events, and mortality, the advantages of dabigatran were greater at sites with poor INR control compared with those with good INR control. For this reason, local standards of care can be expected to determine the degree of benefit derived from newer anticoagulant agents compared with warfarin therapy.

The Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) study, currently under way, will provide a comparison of apixaban and warfarin in stroke prevention in AF.[15] Similarly, the ROCKET-AF study will compare rivaroxaban with warfarin in patients with AF who are at high risk of stroke.[8] Overall, local standards of care are expected to significantly affect the benefits of using new treatment alternatives.

Case Study Discussion: Lucia A.

Lucia A. is a 76-year-old Hispanic woman who was recently diagnosed with AF. She is a Medicare patient. Her medical history includes treatment for hypertension (fixed-dose combination antihypertensive, hydrochlorothiazide/lisinopril 12.5 mg/20 mg once daily). Her blood pressure is 143/84 mm Hg. Lucia lives alone, but she is visited daily by her daughter or granddaughter (who both live nearby). AF raises Lucia's risk of stroke by up to 5-fold. Lucia's $CHADS_2$ score adds up to at least 2 (ie, age of 76 years = 1 point, plus hypertension = 1 point), and this score carries an expected annual stroke rate of 2.54 events per 100 person-years.[16] Given her level of risk for stroke, she should clearly consider anticoagulation therapy. For an AF patient with a $CHADS_2$ score of 2, warfarin is expected to substantially reduce the projected annual rate of thromboembolism from 2.54 to 1.26 events per 100 person-years.[16] Aspirin therapy is not expected to provide adequate stroke protection in a patient with a $CHADS_2$ score of 2 and is not recommended for her level of risk. Lucia has no definite contraindications for warfarin therapy.[1,17] Lucia and her clinician must consider the anticipated benefit against the risks of warfarin therapy. Lucia's ability to take warfarin safely depends on her ability to have regular INR checks and to accurately follow instructions to make changes to warfarin doses when instructed by her anticoagulation clinic. Although Lucia lives alone, she is in close daily contact with her family; their commitment and level of involvement in her care should be ascertained before making a decision to use warfarin. One important consideration is Lucia's risk and her history of falling. Does she have limited mobility? Finally, depending on future availability and affordability, she may

want to consider a direct thrombin inhibitor or a factor Xa inhibitor if she is reluctant to begin warfarin therapy. For example, the US Food and Drug Administration (FDA) has recently approved dabigatran for stroke prevention in patients with AF.[18]

Conclusion

Warfarin is clearly effective in preventing strokes in patients with AF who are at high risk, but it can also provide significant protection in patients with a low risk of stroke. A recent comparison of warfarin therapy with a regimen of clopidogrel plus aspirin reported treatment-specific rates of stroke and major bleeding for patients with AF and a $CHADS_2$ score of 1 and compared the results in patients with a $CHADS_2$ score greater than 1.[19] The study found that even patients with a low risk of stroke (ie, $CHADS_2 = 1$) derived a modest (<1% per year) but significant absolute reduction in stroke accompanied by low rates of major hemorrhage with warfarin. The European Society of Cardiology has recently begun to recommend warfarin use in patients with AF and $CHADS_2$ scores as low as 1, in contrast to the prior recommendation of equivalent consideration of aspirin.[17] However, a number of factors, including significant variability in dose-response, drug and dietary interactions, and a narrow therapeutic window, have influenced some clinicians to underuse warfarin in this patient population.[20] Underuse has subsequently driven a search for alternative orally administered antithrombotic agents that couple efficacy with a lower risk of major bleeding. Several new and emerging anticoagulant agents, such as the factor Xa inhibitors apixaban and rivaroxaban, are in the late stages of development. The direct thrombin inhibitor dabigatran has recently been approved by the FDA for stroke prophylaxis in AF.[18] Results from clinical trials suggest that dabigatran may provide a safe, effective alternative to warfarin in AF. Apixaban was superior to aspirin for stroke prevention in AF[6]; whether it is a viable alternative to warfarin in patients with AF remains to be seen. Trials designed to make clinical comparisons between warfarin and rivaroxaban in AF are under way.[8] The possibility of eliminating the need for continual INR testing is expected to offset a substantial portion of the cost of these new agents.

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Authorship Information: Concept and design (CPC, ECS); drafting of the manuscript (ECS); critical revision of the manuscript for important intellectual content (CPC, ECS); administrative, technical, or logistical support (ECS); and supervision (CPC, ECS).

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