Current Treatment Options in Cardiovascular Medicine (2011) 13:361–369
DOI 10.1007/s11936-011-0139-4

Arrhythmia

Pharmacologic Strategies for the Prevention of Stroke in Patients With Atrial Fibrillation

*Greg Flaker, MD**
Richard Weachter, MD

Address
*Division of Cardiovascular Medicine, University of Missouri-Columbia, Five Hospital Drive, CE306, Columbia, MO 65212, USA
Email: flakerg@health.missouri.edu

Published online: 6 July 2011

Opinion statement

Stroke is a dreaded complication of atrial fibrillation. In the past, preventive therapy included aspirin and oral anticoagulation. Selected patients who are not suitable for oral anticoagulation may benefit from the addition of clopidogrel with aspirin. This combination, when compared with aspirin, offers a reduced risk of stroke at a cost of more major bleeding. We use this therapy in patients with atrial fibrillation who have unstable coronary syndromes or in patients who receive coronary artery stents who are not good candidates for "triple therapy" with aspirin, clopidogrel, and warfarin. The duration of therapy is tempered by many variables. In the case of coronary stents, we ask the interventionalist to consider a bare metal stent to shorten the duration of need for clopidogrel plus aspirin. After several months of combination therapy, we stop this therapy and begin warfarin therapy. Dabigatran is commercially available in the United States. In patients who have difficult to control International Normalized Ratio (INR) values or who do not wish to have regular coagulation monitoring, dabigatran offers a huge advantage. The benefit seems less if the INR is consistently within range. We are impressed with the superior reduction in stroke and systemic embolism with 150 mg of dabigatran twice daily compared to warfarin and also its low risk of intracranial hemorrhage. The results of clinical trials involving factor Xa agents are now being presented. How these agents fit into the marketplace remains to be seen but they will offer clinicians additional therapy for stroke prevention in atrial fibrillation.

Introduction

Oral anticoagulation with a vitamin K antagonist has been the preferred therapy for stroke prevention in higher-risk patients with atrial fibrillation (AF). Aspirin has been recommended for lower-risk patients or for patients in whom warfarin is not suitable. Placebo-controlled trials supporting this recommendation show that stroke or systemic embolism is reduced 64% with adjusted-dose warfarin and by 21% with aspirin [1]

(Fig. 1). These recommendations, with minor revisions, have been included in published guidelines for nearly 20 years [2]. Now, with the advent of new anticoagulants, pharmacologic therapy for stroke prevention in AF is changing. New therapies offer the prospect of more effective stroke prevention with similar or lower rates of major bleeding. Importantly, they will not require regular monitoring. The prompt onset of action will provide adequate anticoagulation over a shorter period of time than warfarin. The prompt offset of action will allow performance of surgery or invasive procedures without much delay. These agents will have fewer food and drug interactions. This article will review the results of recent clinical trials involving new pharmacologic agents for stroke prevention in AF.

Antiplatelet therapy

A variety of abnormalities of both hemostasis and platelet function occur with AF. Markers of intravascular thrombogenesis, including fibrin D-dimer [3–5] and prothrombin fragment F 1+2 [6], are consistently elevated in patients with AF. Other factors such as fibrinogen, a measure of clotting and rheology, and von Willebrand factor, a measure of endothelial function, have been reported to be either elevated [4, 5] or normal [7, 8] in patients with AF. Fibrinogen and von Willebrand factor levels may be affected by the presence of underlying cardiovascular disease [9], which may coexist with AF. β-Thromboglobulin and soluble P-selectin, markers of platelet activation, are also elevated in AF [10, 11], but measures of platelet aggregation are not elevated in patients with AF. Vitamin K antagonists and platelet inhibitors affect these markers of thrombogenesis and platelet function in different ways (Table 1) [4, 7, 11].

Several biomarkers of hypercoagulability are also associated with adverse cardiac events in patients with AF. In a Japanese study, elevated levels of D-dimer were associated with a higher incidence of thromboembolic events and cardiovascular events [12]. Other biomarkers, including prothrombin fragment 1+2, fibrinogen, and β-thromboglobulin, have not predicted stroke [13]. In the Rotterdam study, plasma von Willebrand factor, fibrinogen, and soluble P-selectin failed to predict stroke in patients with AF, but elevated levels of P-selectin did predict cardiac mortality in patients with AF [8].

In summary, AF is associated with abnormalities of hemostasis and abnormalities of platelet function. Some of these markers predict adverse cardiovascular events. Because aspirin has a modest benefit in stroke prevention in patients with AF, would the addition of clopidogrel, a more potent inhibitor of platelets, added to aspirin translate into a reduction of stroke?

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events W (ACTIVE W) trial was a prospective, randomized, open-treatment trial designed to assess whether aspirin 75 to 100 mg/day plus clopidogrel 75 mg/day was non-inferior to oral anticoagulation with a target International Normalized Ratio (INR) of 2.0 to 3.0 [14]. Following the randomization of 6,706 patients, ACTIVE-W was terminated due to the clear superiority of oral anticoagulation therapy. Over a median follow-up duration of 1.28 years, dual antiplatelet therapy recipients experienced an almost a 1.5-fold increased risk of the primary endpoint of stroke, non-central nervous system (CNS) systemic embolus, myocardial infarction (MI), or vascular death compared with oral anticoagulation therapy recipients (5.60% per year vs 3.93% per year) and a 1.7-fold increased risk of stroke (2.39% per year vs 1.40% per year). The rates of major bleeding were similar between the treatment arms.

Although ACTIVE W established the superiority of oral vitamin K antagonists over clopidogrel plus aspirin, a number of patients with AF still do not receive oral anticoagulation therapy for a variety of reasons. To address this important group of patients, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events A (ACTIVE A) randomized patients with AF who were at increased risk but who were unsuitable for oral anticoagulation to either aspirin or aspirin plus clopidogrel [15••]. Following a median 3.6 years of follow up, clopidogrel plus aspirin decreased the relative risk of the primary endpoint of stroke, MI, non-CNS embolism, or death from vascular causes by 11% compared with aspirin alone (6.8% per year vs 7.6% per year; $P<0.01$). The majority of this benefit arose from a 28% reduction in the relative risk of stroke in clopidogrel-plus-aspirin recipients (2.4% per year vs 3.3% per year; $P<0.001$). The rate of MI was also lower in the clopidogrel-plus-aspi-

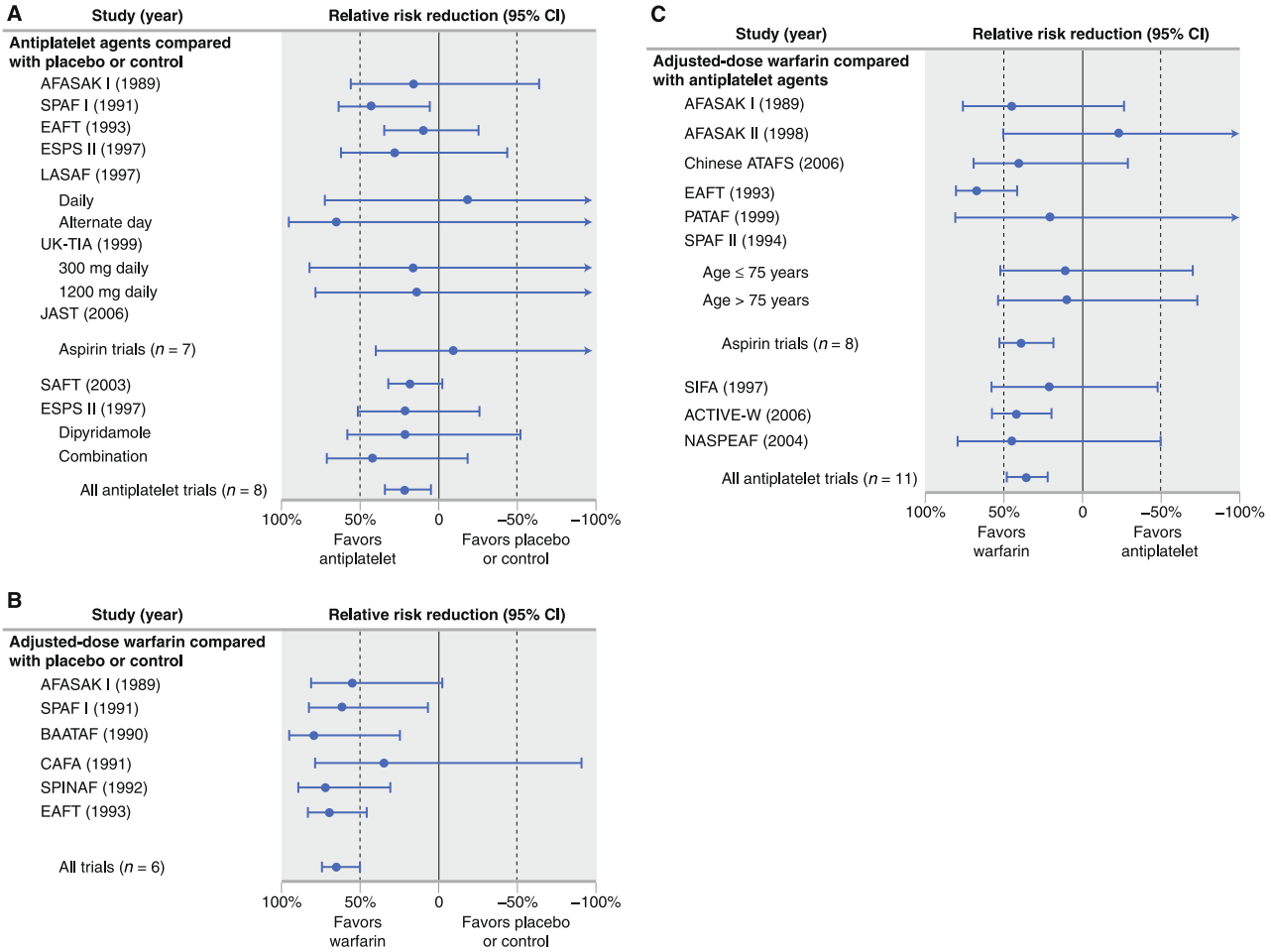

Figure 1. Relative effects of anti-thrombotic therapies on all stroke from randomized trials in patients with atrial fibrillation [16]. **a** Antiplatelet agents compared with placebo or no treatment in eight randomized trials. **b** Adjusted-dose warfarin compared with placebo or no treatment in six randomized trials. **c** Adjusted-dose warfarin compared with antiplatelet agents in 11 randomized trials.

rin arm (0.7% per year vs 0.9% per year in the aspirin arm), but the risk reduction was not statistically significant (P=0.08). However, the reduction in cardiovascular events came at the price of a significant increase in the risk of major bleeding, which occurred at a rate of 2.0% per year in clopidogrel-plus-aspirin recipients compared to 1.3% per year in aspirin-only recipients (P<0.001).

The use of clopidogrel for stroke prevention in AF is currently not approved for use in the United States. Because of the expense of clopidogrel and concern about bleeding, this therapy is currently used infrequently in patients with risk factors for stroke. The 2011 focused Update on the Management of Patients with Atrial Fibrillation notes that the addition of clopidogrel to aspirin could be considered in patients with AF in whom oral anticoagulation with warfarin is not suitable [16].

Direct thrombin inhibitors

Thrombin is of central importance to coagulation. It converts fibrinogen to fibrin. It activates coagulation factors V, VIII, and XI. It stimulates platelets. Thrombin inhibitors therefore have an impact on more than

Table 1. Impact of warfarin and clopidogrel plus aspirin on hemostatic and platelet function tests in atrial fibrillation

	AF	Warfarin	C+ASA
Indices of thrombogenesis			
Fibrin D Dimer	↑	↓	–
F1+2	↑	↓	–
Platelet activation			
β-Thromboglobulin	↑	↓	–
Soluble P-selectin	↑	↑	–
Platelet aggregation			
ADP response	–	–	↓
Epinephrine response	–	–	↓

AF atrial fibrillation; *C+ASA* clopidogrel plus aspirin

just thrombin. One commonly used thrombin inhibitor is heparin, which has established benefit in a wide variety of disorders related to thrombus formation. Heparin is administered parenterally and requires antithrombin as a cofactor to bind at thrombin sites, thereby acting indirectly on thrombin. Direct thrombin inhibitors, including ximelagatran and dabigatran, act independently of antithrombin and bind to thrombin sites, thereby inhibiting coagulation. Direct thrombin inhibitors also reduce thrombin-mediated platelet activation. Two direct thrombin inhibitors, ximelagatran and dabigatran, have undergone extensive clinical trials for stroke prevention in atrial fibrillation.

In the Stroke Prevention with the Oral Direct Thrombin Inhibitor Ximelagatran Compared with Warfarin in Patients with Non-valvular Atrial Fibrillation (SPORTIF III) trial, ximelagatran was compared with adjusted dose warfarin with an INR goal of 2 to 3. Ximelagatran was associated with a 29% reduction in stroke or systemic embolism compared to warfarin. The rates of major bleeding were similar between groups, but combined minor and major hemorrhages were lower with ximelagatran compared with warfarin [17]. The SPORTIF V trial followed an identical protocol but was performed in North America with a double-blinded treatment assignment. In this study, ximelagatran was associated with a similar rate of stroke or systemic embolism compared with adjusted-dose warfarin (1.6% per year vs 1.2% per year; P = not significant) and was within the pre-specified range of non-inferiority [18]. Because of hepatotoxicity, ximelagatran was withdrawn from the market place.

Dabigatran, another direct thrombin inhibitor, has not been associated with hepatotoxicity. In the Ran-

Table 2. Comparative pharmacology: dabigatran and warfarin

	Dabigatran	Warfarin
Target	IIa	Multiple
Half-life	12–17 h	40 h
Steady state	2–3 d	4–5 d
Dosing	150 mg twice daily[a]	Daily, adjusted
Renal metabolism	80%	0
Interactions	? amiodarone, verapamil, quinidine	Multiple
Monitoring	No	Yes

[a]For patients with a creatine clearance of 15–30 cm^3/min, the dose is 75 mg twice daily

domized Evaluation of Long-term Anticoagulation Therapy (RE-LY), dabigatran (110 mg twice daily and 150 mg twice daily) was compared with open-label warfarin in patients with AF at increased risk for stroke [19••]. In this trial dabigatran given at 110 mg twice daily had a 1.5% per year risk of stroke or systemic embolism compared to 1.7% per year in the warfarin group ($P=0.30$). The risk of major bleeding was 2.9% per year with dabigatran 110 mg twice daily versus 3.6% per year in warfarin ($P=0.003$). Dabigatran 150 mg twice daily had a 1.1% per year risk of stroke or systemic embolism ($P<0.001$ compared to warfarin) and a 3.3%'year risk of major bleeding ($P=0.32$ compared to warfarin). The yearly mortality rate was 4.1% with warfarin, 3.75% with dabigatran 110 mg twice daily, and 3.6% with dabigatran 150 mg twice daily. Both doses of dabigatran were associated with a lower rate of intracranial hemorrhage compared to warfarin.

In summary, dabigatran 150 mg twice daily offered improved efficacy in stroke prevention with a similar risk of major bleeding compared to warfarin. Dabigatran 110 mg twice daily had similar efficacy with a lower risk of major bleeding compared to warfarin. There were no statistically significant differences between the groups in terms of overall mortality. Based on this large study, dabigatran has been approved in the United States for prevention of stroke and systemic embolism in patients with non-valvular AF. However the recommended dosing is different than that used in RE-LY. For patients with a creatinine clearance of >30 cm^3/min, a dose of 150 mg twice daily is recommended. For patients with a creatinine clearance of 15 to 30 cm^3/min, a dose of 75 mg twice daily is recommended. Dosing recommendations for patients with a creatinine clearance <15 cm^3/min or for patients on dialysis cannot be provided. Important differences between dabigatran and warfarin are shown in Table 2.

It is clear that dabigatran represents a tremendous step forward in the field of anticoagulation. However, clinicians using dabigatran should be aware of several caveats with this therapy. Dyspepsia occurred in 11% to 12% of patients. This may be due to the tartaric acid core, which helps improve absorption of the drug, although the amount of extra acidity is small. The coating of dabigatran is easily altered. The medication should not be broken up or disrupted and mixed with foods. Once the bottle is opened, capsules should be used within 30 days. Many elderly patients may have care givers sort medications in a pill dispenser to improve compliance. This is not recommended with this medication. Gastrointestinal (GI) bleeding was higher with dabigatran compared with warfarin and dabigatran was more frequently discontinued compared with warfarin. Patients with upper gastrointestinal symptoms were often advised to take dabigatran with meals or with proton pump inhibitors or H2 antagonists. Trough levels of dabigatran were not affected by these agents.

There has been concern about the increased frequency of MIs with ximelagatran compared to warfarin. In RE-LY, MI rates were slightly higher in patients receiving dabigatran 110 mg twice daily (0.8% per year) and dabigatran 150 mg twice daily (0.8% per year) compared to warfarin (0.6% per year). Previous trials involving direct thrombin inhibitors have had mixed results. In SPORTIF III, more MIs were noted in patients treated with ximelagatran compared to warfarin (1.1% per year vs 0.6% per year). In SPORTIF V, fewer MIs were noted in patients treated with ximelagatran compared to warfarin (1% per year vs 1.4% per year). In a venous thromboembolism trial comparing ximelagatran with enoxaparin and warfa-

Table 3. Comparative pharmacology: factor Xa inhibitor

	Apixaban	Rivaroxaban
Target	Xa	Xa
Half-life	9–14 h	5–9 h
Dosing	Twice daily	Daily
Renal metabolism	25%	65%
Interactions	Minor	Minor
Peak to trough ratio	3:1 (twice daily)	15–20:1 (daily)

rin, an increase in the rate of symptomatic myocardial ischemia requiring hospitalization, several of which turned out to be cases of MIs, was reported with ximelagatran [20]. When ximelagatran was used in patients receiving extended therapy (beyond 6 months following venous thromboembolism), the risk of a fatal MI was low (0.16%) in patients treated with ximelagatran and placebo [21]. Ximelagatran reduced recurrent MI compared with placebo when administered after MI [22]. Direct thrombin inhibitors were also associated with a reduction in MIs when incorporated in the management of acute coronary syndromes [23]. Dabigatran has not been associated with an increase in cardiovascular events when given for deep venous thrombosis after orthopedic surgery [24–26]. In summary, studies suggesting an increase in MIs with ximelagatran have generally been noted when ximelagatran was compared to warfarin. Some investigators have suggested that warfarin, by affecting multiple coagulation parameters, may be a more effective agent in MI prevention than previously realized.

Up to 80% of dabigatran is excreted via a renal pathway, and clinical trials including RE-LY excluded patients with a creatinine clearance of <30 cm^3/min. It is also metabolized by the P-glycoprotein system, which reduces GI absorption, enhances bile and urine elimination, and prevents entry into the CNS. The latter factor may be the reason for the very low rate of intracranial bleeding associated with dabigatran. Alteration of GI absorption of dabigatran may also allow higher local levels in the gut, resulting in the excess GI bleeding risks noted previously. The use of dabigatran with potent inducers of the P-glycoprotein system should be avoided. Certain cardiac medications inhibit the P-glycoprotein pathway, including quinidine, verapamil, amiodarone, and dronedarone. No important changes in trough levels of dabigatran were observed in patients who received verapamil or amiodarone. Currently, these medications do not require dose adjustment. However, these agents may result in higher dabigatran levels and may potentially lead to excess bleeding, so the clinician should be aware of this possibility. There is little experience thus far with dronedarone and dabigatran.

Although monitoring is not required for dabigatran, there is a linear dose relationship between the ecarin clotting time and the thrombin clotting time with therapeutic concentrations of dabigatran [27], but the use of these tests as a monitoring tool requires more clarification. In cases of excess bleeding, there is no recommended antidote.

Dabigatran is more expensive than warfarin. The current wholesale cost in the United States is about $6.75 per day for both 150 mg twice daily or 75 mg twice daily. The costs take into account the price for research and development as well as the reduction in clinical outcomes and the advantage of no INR monitoring. Dabigatran 150 mg twice has been estimated to cost $45,372 per quality-adjusted life-year compared with warfarin, which is generally considered cost effective. This analysis was performed before the cost of dabigatran was established, and for this analysis the cost of dabigatran was assumed to be $13 per day. In this model, this dose of dabigatran yielded an additional 0.56 quality-adjusted life-years compared with warfarin [28].

A frequently asked question is should a patient with a stable INR be converted to dabigatran? The available information suggests that the risk of stroke and systemic embolism is not significantly different in patients receiving dabigatran 150 mg twice daily and well-managed warfarin. Major bleeding rates are similar in patients who receive dabigatran 150 mg twice daily and well-managed warfarin. The clinician has options in patients who consistently maintain an INR in the 2 to 3 range [29].

Factor Xa inhibitors

Factor X is synthesized in the liver. Factors IX and VII, along with cofactors Factor VIII and tissue factor, activate Factor X, forming Factor Xa. Factor Xa converts prothrombin to thrombin. Factor Xa is potent. One molecule of factor Xa can generate 1000 molecules of thrombin, which makes Factor Xa an attractive target for thrombus inhibition. Specific inhibitors of Factor Xa have been developed. These agents include idraparinux, apixaban and rivaroxaban. Some exhibit anti-Xa activity with anti-thrombin III (heparin). So far, three main trials have been published involving the use of factor Xa inhibition in stroke prevention in AF.

Idraparinux Idraparinux is a factor Xa inhibitor administered by a fixed subcutaneous dose on a weekly basis. In A Multicenter, Randomized, Open-label, As-

sessor Blind, Non-inferiority Study Comparing the Efficacy and Safety of Once-weekly Subcutaneous Idraparinux (SR34006) With Adjusted-dose Oral Vitamin-K Antagonists in the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation (AMADEUS), patients with AF at risk for thromboembolism were randomized to receive a 2.5-mg fixed weekly subcutaneous dose of idraparinux or vitamin K antagonists. Idraparinux was found to be non-inferior to conventional anti-coagulation but the trial was stopped prematurely due to excessive bleeding with idraparinux [30].

Apixaban Apixaban is a direct factor Xa inhibitor that reaches a maximum plasma concentration within 0.5 to 2 h of administration. The half-life is about 8 to 15 h. Apixaban is mainly metabolized by the liver CYP3A4 system, with about 30% renal excretion.

The use of apixaban in patients with AF who were unsuitable for oral anticoagulants was tested in the Apixaban versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double Blind Trial (AVERROES). These patients with AF and at least one other risk factor were randomized to either aspirin 81 to 324 mg daily or apixaban 5 mg twice daily. A dose of 2.5 mg twice daily of apixaban was used in patients with two of the following: age >80 years, weight <60 kg, or serum creatinine >1.5 mg/dL. The results of this study showed that apixaban was associated with a 54% relative risk reduction in systemic embolism or stroke compared to aspirin. Remarkably, the risk of major bleeding was similar between the two agents. Permanent discontinuation of study medicine was actually less frequent with apixaban compared to aspirin [31].

Rivaroxaban Rivaroxaban is a direct factor Xa inhibitor with different pharmacologic properties compared with apixaban (Table 3). Rivaroxaban has a maximum plasma concentration occurring in 0.5 to 3 h and a half life of 3 to 9 h. About 70% is metabolized in the urine. Other important metabolism occurs by the liver via the CYP3A4 pathway and the CYP2J2 pathway.

In the Rivaroxaban-Once Daily, Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study, patients with a history of a stroke or at least two additional risk factors were randomized to either 20 mg once daily of rivaroxaban or dose-adjusted warfarin with a target INR of 2.5. In contrast to RE-LY, the ROCKET-AF study was a double-blind, double-dummy trial. The average CHADS2 score was nearly 3.5. The primary efficacy endpoint was a composite of all-cause stroke or a non-CNS systemic embolism. The primary safety endpoint was a composite of clinically relevant non-major bleeding events. As specified in the design paper, the investigators assessed primary efficacy on a per-protocol basis. In other words, only patients who received study drug will be compared to warfarin for non-inferiority, unless subjects have had a major protocol violation before a study endpoint. If non-inferiority was satisfied, superiority was tested on the per-protocol patients and then in an intention-to-treat analysis [32].

ROCKET-AF was presented at the 2010 American Heart Association meeting. The results demonstrated that rivaroxaban was superior to warfarin in patients who were taking the study medication. Rivaroxaban did not achieve superiority in an intention-to-treat analysis. The drug had a comparable bleeding risk to warfarin with similar rates of bleeding and adverse events. There was less intracranial bleeding and less fatal bleeding with rivaroxaban compared to warfarin. Some have questioned the adequacy of warfarin anticoagulation in ROCKET-AF because the mean time in therapeutic range in warfarin-treated patients was only 57%. Nevertheless this study introduces another group of agents to clinicians who want to reduce stroke risk in patients with AF [33].

Other studies Two additional studies in stroke prevention in atrial fibrillation are ongoing. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, apixaban is being compared to warfarin for stroke prevention in AF. In the Evaluation of the Novel Factor Xa Inhibitor Edoxaban Compared with Warfarin in Patients with Atrial Fibrillation (ENGANGE-AF TIMI 48) trial, the factor Xa inhibitor edoxaban is being compared with warfarin in patients with a CHADS score >2.

Disclosure

G. Flaker has received consulting fees from Sanofi Aventis and Bristol-Myers Squibb. He has received support for travel to meetings from Boehringer Ingelheim and Bristol-Myers Squibb, and his institution has received grant money from Boehringer Ingelheim and Bristol-Myers Squibb. R. Weachter reports no potential conflict of interest relevant to this article.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Hart RG, Lesly AP, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Int Med. 2007;146(12):857–67.
2. Laupacis A, Albers G, Dunn M, Feinberg W. Antithrombotic therapy in atrial fibrillation. Chest. 1992;102(suppl):426S–33S.
3. Kumagai K, Fukunami M, Ohmori M, et al. Increased intracardiovascular clotting in patients with chronic atrial fibrillation. J Am Coll Cardiol. 1990;16:377–80.
4. Gustafsson C, Blomback M, Britton M, Hamsten A, Svensson J. Coagulation factors and the increased risk of stroke in nonvalvular atrial fibrillation. Stroke. 1990;21:47–51.
5. Lip GY, Lowe GD, Rumley A, Dunn FG. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Br Heart J. 1995;73:527–33.
6. Asakura H, Hifumi S, Jokaji H, et al. Prothrombin fragment F1+2 and thrombin-antithrombin III complex are useful markers of the hypercoagulable state in atrial fibrillation. Blood Coagul Fibrinolysis. 1992;3:469–73.
7. Kamath S, Blann AD, Chin BS, et al. A study of platelet activation in atrial fibrillation and the effects of antithrombotic therapy. Eur Heart J. 2002;23:1788–95.
8. Heeringa J, Conway DS, van der Kuip DA, et al. A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation: the Rotterdam Study 1990–1999. J Thromb Haemost. 2006;4:1944–9.
9. Feng D, D'Agostino RB, Silbershatz H, et al. Hemostatic state and atrial fibrillation (The Framingham Offspring Study). Amer J Cardiol. 2001;87:168–71.
10. Lip GYH, Lip PL, Zarifis J, et al. Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose of warfarin and aspirin. Circulation. 1996;94:425–31.
11. Kamath S, Blann AD, Chin BS, Lip GY. A prospective randomized trial of aspirin-clopidogrel combination therapy and dose-adjusted warfarin on indices of thrombogenesis and platelet activation in atrial fibrillation. J Am Coll Cardiol. 2002;40:484–90.
12. Sadangara T, Sadanaga M, Ogawa S. Evidence that d-Dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. JACC. 2010;55:2225–31.
13. Feinberg WM, Pearce LA, Hart RG, et al. Markers of thrombin and platelet activity in patients with atrial fibrillation: correlation with stroke among 1531 participants in the stroke prevention in atrial fibrillation III study. Stroke. 1999;30:2547–53.
14. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903–12.
15.•• Connolly SJ, Pogue J, Hart RG, et al.: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066–78.

This citation reopens the possibility that platelet function is an important factor for stroke in AF.

16. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation (Updating the 2006 Guideline)ACC/AHA guidelines. JACC 2011;57:223–42.
17. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet. 2003;362:1691–8.
18. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA. 2005;293(6):690–8.

19.•• Connolly SJ, Ezekowitz MD, Yusuf S, et al.: Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009;361(12):1139–202. Correction NEJM 2010;363:11875–6.

This is a landmark paper demonstrating the superiority of 150 mg twice daily of dabigatran compared to warfarin for stroke prevention in AF.

20. Fiessinger JN, Huisman MV, Davidson BL, et al. Ximelagatran vs. low molecular weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. JAMA. 2005;293:681–9.
21. Shulman S, Wahlander K, Lundstrom T, THRIVE III Investigators, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med. 2003;248:1713–21.
22. Wallentin L, Wilcox R, Weaver W, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. Lancet. 2003;362(9386):789–97.
23. The Direct Thrombin Inhibitors Investigators. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. Lancet. 2002;359(9303):294–302.
24. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. Lancet. 2007;370(9591):949–55.
25. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatrann etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolisms after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5 (11):2178–85.
26. The RE-MOBILIZE Writing committee. The oral thrombin inhibitor dabigatran etexilate vs. the North American enoxaparin regimen for the prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty. 2009;24(1):1–9.
27. Stangier J, Rathgen K, Stahle H, et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in health male subjects. Br J Clin Pharmacology. 2007;64(3):292–303.
28. Freeman J, Zhu R, Owens DK et al. Cost Effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Annals Int Med 2010.
29. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ration control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010;376:975–83.
30. The AMADEUS Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomized, open-label, non-inferiority trial. Lancet. 2008;371:315–21.
31. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation unsuitable for vitamin K antagonists. New England J Feb 10, 2011;364:806–17.
32. The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET AF study. Amer Heart J. 2010;159:340–7.
33. ROCKET-AF. Presented at the American Heart Association meeting 2010.