An Update on Antithrombotic Therapy in Atrial Fibrillation: The Role of Newer and Emergent Drugs

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with potentially dreadful cardioembolic complications such as stroke. The risk of stroke is stratified based on the patient's comorbid conditions using several scoring systems. Patients are treated with oral anticoagulation using warfarin or aspirin based on their cardioembolic stroke risk. Although warfarin has been the only effective therapy, it is underutilized clinically due to concern for multiple drug-to-drug and drug-to-food interactions and hemorrhagic complications. Dual antiplatelet therapy with aspirin and clopidogrel has been studied as a potential alternative anticoagulant for AF patients; however, the combination of aspirin and clopidogrel was noted to be inferior to warfarin in preventing strokes, with an increased risk of bleeding. As a result, newer anticoagulant agents, including direct thrombin inhibitors, direct and indirect factor Xa inhibitors, and vitamin K antagonists, have been developed and evaluated in AF patients. Results from a recent study demonstrated that high-dose dabigatran, a direct thrombin inhibitor, was superior to warfarin in preventing stroke and systemic embolism with similar bleeding risk. It ultimately received approval by the US Food and Drug Administration for stroke prophylaxis for nonvalvular AF patients. There are several other direct factor Xa inhibitors currently under study. Dabigatran may be considered in AF patients who are intolerant to warfarin or unwilling or unable to follow-up with frequent laboratory monitoring. Other newer anticoagulant agents also provide us with possible suitable alternatives to warfarin, and their clinical use will depend on the results from ongoing studies.

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KEY WORDS

Atrial fibrillation • Antithrombotic therapy • Stroke prevention • Factor Xa inhibitors

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is especially prevalent in the elderly population. The number of AF patients is expected to double by 2050.[1,2] AF is associated with many complications, including cardioembolic strokes.[3] Patients with both valvular AF (eg, mitral stenosis) and nonvalvular AF are at increased risk of embolic strokes. Stroke related to AF accounts for approximately 15% of all the strokes in the United States and often results in severe functional deficit or death.[4]

Pharmacologic antithrombotic strategies, including antiplatelet agents and oral anticoagulants, are used to prevent cardioembolic complications. Therapeutic anticoagulation with warfarin reduces the frequency and severity of strokes and the risk of death from stroke.[5] Its usage in the AF population has been limited due to the need for frequent laboratory monitoring to maintain therapeutic levels within a narrow range, multiple food-to-drug and drug-to-drug interactions, and the risk of hemorrhagic complication (this is particularly true in the elderly population in whom there is concern regarding bleeding complications; however, the risk-to-benefit ratio is even more supportive of anticoagulation).[6,7] Because of these issues, newer oral anticoagulants have been studied and developed. This review provides an overview of new oral anticoagulants and examines the available data regarding the clinical usefulness of these agents.

Risk Stratification for Cardioembolic Events in AF

AF patients have different cardioembolic risks and it is particularly important to identify high-risk patients who may benefit from intense antithrombotic therapy for both primary and secondary prevention. $CHADS_2$ (congestive heart failure; hypertension: blood pressure consistently > 140/90 mm Hg; age ≥ 75 years; diabetes mellitus; prior stroke or transient ischemic attack [TIA]) risk score index is commonly used to categorize AF patients into different risk groups based on their comorbid conditions (Table 1).[8,9] Therapeutic anticoagulation with warfarin is indicated in high-risk AF patients (score of ≥ 2). On the other hand, acetylsalicylic acid may be chosen as the sole antithrombotic agent in low- to intermediate-risk AF patients (score of 0-1), although oral anticoagulation with warfarin is still preferred. Clinicians should have a thorough discussion with the intermediate-risk AF patients regarding the benefits and the risks of each therapy in order to individualize the antithrombotic therapy in this particular group of patients.[10] Antithrombotic therapy may be deferred in lone AF patients or in patients who have contraindication to antithrombotic therapy.[11] The $CHADS_2$ scoring system is a well-validated system; however, it has several shortcomings, such as omission of some important risk factors (thyrotoxicosis, female sex, coronary artery disease). It also categorizes more patients into the intermediate-risk group. Subsequently, researchers have been evaluating other risk stratification systems in order to better classify AF patients into different risk groups.

The CHA_2DS_2-VASc score (Table 1) was recently proposed as a better risk stratification scheme for predicting thromboembolic events. The new schema adopted the same five major risk factors

TABLE 1

$CHADS_2$ Index to Calculate Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation

$CHADS_2$ Risk Criteria	Score
Congestive heart failure	1
Hypertension	1
Age > 75 years	1
Diabetes mellitus	1
Prior **s**troke or transient ischemic attack	2

Stroke Risk Based on $CHADS_2$ Score

$CHADS_2$ Score	Adjusted Stroke Rate (% per year)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

AF, atrial fibrillation.

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considered by the $CHADS_2$ score with the addition of three new risk factors (history of vascular disease, age 65-74 years, and female sex). Each risk factor is assigned a 1-point score with the exception of age > 75 years and prior history of stroke or TIA, which are assigned 2 points each. Patients are categorized into high-, intermediate-, and low-risk for embolic strokes based on total scores (score of 2 or more implies high stroke risk, whereas scores of 1 and 0 are indicative of intermediate and low risk). The treatment recommendations based on embolic stroke risk are similar to the $CHADS_2$ system. The Euro Heart Survey found that the CHA_2DS_2-VASc score had a modestly enhanced predictive value when studied in a real-life cohort of over 1000 AF patients.[12] In the Danish Registry analysis, CHA_2DS_2-VASc score was better at identifying patients who were truly at high risk for cardioembolic strokes.[13] Compared with the $CHADS_2$ scoring system, women and those > 75 years with AF who were proposed to be intermediate-risk are now placed into a high-risk category with a recommendation for full anticoagulation. The current guidelines of the European Society of Cardiology emphasize the use of the CHA_2DS_2-VASc scoring system for a more comprehensive assessment of the risk in patients with $CHADS_2$ scores of 0 to 1.[14] This is further supported by recent findings from a study performed in patients after catheter ablation for AF that showed that the CHA_2DS_2-VASc scheme further identified a higher-risk cohort from those with lower $CHADS_2$ scores (0-1). This study showed that of the 460 patients with $CHADS_2$ scores of 0 to 1, 98 patients were identified with a CHA_2DS_2-VASc score ≥2 and were subsequently found to have an event rate of 7.1%, compared with 362 patients with a CHA_2DS_2-VASc score of 0 to 1 who had an event rate of 1.1% after catheter ablation.[15]

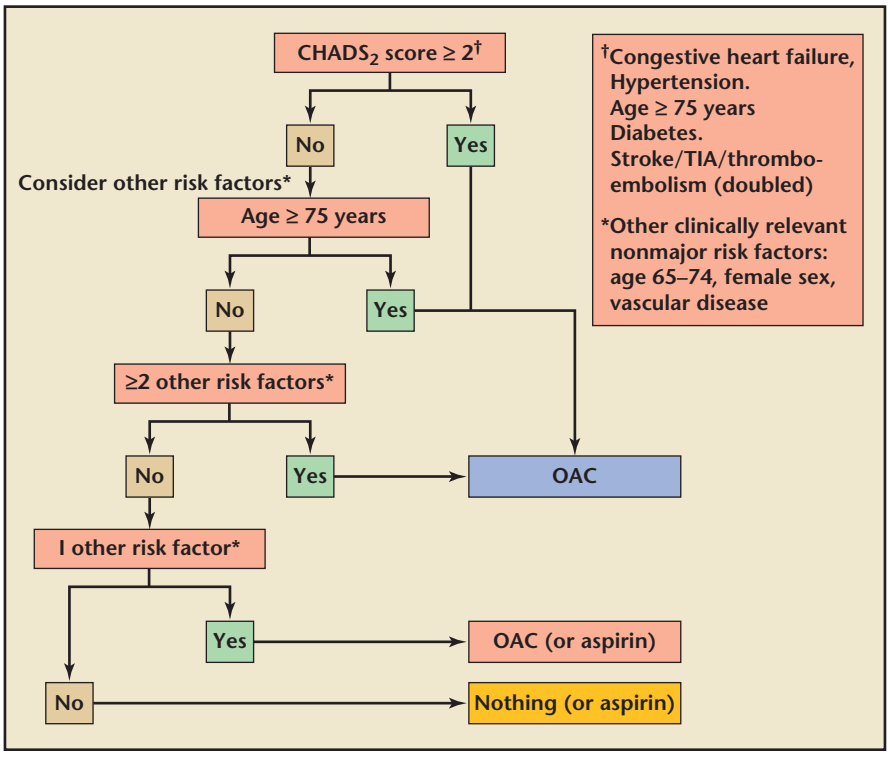

Figure 1. Flowchart demonstrating the clinical application of the CHA_2DS_2-VASc risk stratification scheme. OAC, oral anticoagulant; TIA, transient ischemic attack. Adapted with permission from *Eur Heart J.* 2010;31:2385.

Although the CHA_2DS_2-VASc scheme has been recommended by the European Society of Cardiology in its latest AF practice guidelines (Figure 1),[14] its acceptance in clinical practice in the United States has yet to be established.

Strategies for Stroke Prophylaxis in AF: Old and Current Treatment Options

Because AF is an independent risk factor for catastrophic embolic stroke, various medications (eg, antiplatelet and anticoagulant agents) have been studied as potential preventive strategies. Therapeutic anticoagulation is the only treatment that has been proven to reduce the risk of embolic phenomenon and mortality in AF patients (Figure 2).[8] Available data from large randomized trials showed that warfarin reduced the risk of stroke or systemic embolism by about two-thirds when compared with no treatment and by 30% to 40% when compared with acetylsalicylic acid in high-risk AF patients.[8,16-18] Meta-analysis of stroke prevention in 2600 AF patients showed warfarin (with a therapeutic International Normalized Ratio [INR] of 2-3) reduced stroke by 62% with the absolute risk reduction of 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[7] Another study demonstrated that subtherapeutic INR (INR < 2) resulted in a higher risk of stroke. The odds ratio for stroke increased to 2 when INR was < 1.7 and the ratio became 3.3 when INR was 1.5.[19] Results from these studies demonstrated that therapeutic anticoagulation is the treatment of choice for stroke prophylaxis in the AF population and emphasized the importance of achieving an appropriate INR goal in order to prevent stroke.

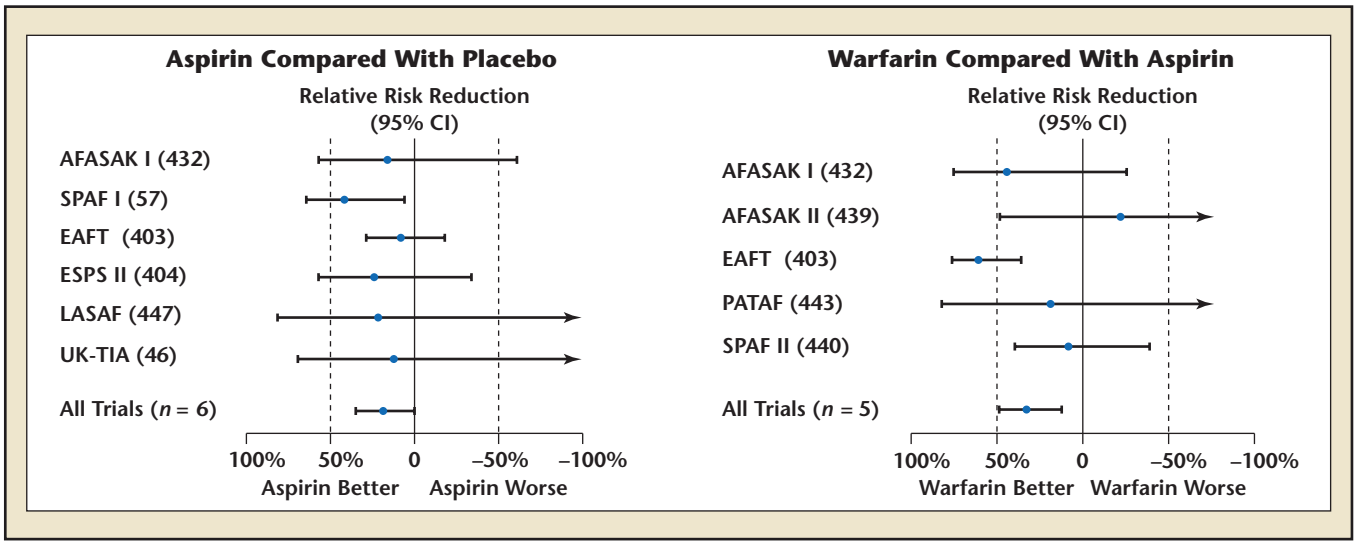

Figure 2. Effects on all strokes (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation: aspirin compared with placebo and warfarin compared with aspirin. AFASAK, Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, the United Kingdom Transient Ischemic Attack Aspirin Trial; PATAF, Prevention of Atrial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. From Fuster V et al, "ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: Full Text: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society," *Europace*, 2006;8:651-745, by permission of Oxford University Press.[8]

Warfarin Therapy

Warfarin is a potent, noncompetitive inhibitor of the vitamin K epoxide reductase complex 1 (VKORC1) and it prevents gamma carboxylation of prothrombin, factor II, VII, IX, and X, and protein C and S.[20] Although treatment with warfarin is clearly beneficial in reducing the risk of stroke and mortality in AF patients, underutilization of therapeutic warfarin for high-risk AF patients has been noted in a recent systemic review of 54 studies. In this analysis, investigators evaluated the treatment level for each study. Treatment level was based on the percentage of patients who were eligible for oral anticoagulation due to elevated stroke risk compared with the percentage treated. A majority of the studies had a treatment level (defined as time in therapeutic range [TTR]) of $<70\%$, which confirmed the previously known fact that therapeutic anticoagulation is often not achieved for stroke prophylaxis and there is a need to critically evaluate why warfarin is underutilized.[21]

Warfarin has several properties that limit its widespread usage. It has a slow onset of action, narrow therapeutic window, variable cytochrome p450 (CYP450)-dependent metabolism, and significant number of drug-to-food and drug-to-drug interactions (Table 2).[22-24] Because of these problems, it is mandatory for patients to have frequent INR monitoring and dosage adjustment in order to maintain therapeutic level, and to notify the monitoring physician when there are changes in medication or diet. In a community study of AF patients over a total of 4.5 years, therapeutic INR was achieved less than one-third of the time when it was evaluated on follow-up visits. These patients had INRs in the subtherapeutic range 50% of the time and supratherapeutic levels 25% of the time.[25] Aside from suboptimal therapeutic levels and the associated thrombotic and hemorrhagic complications, AF patients also incurred considerable costs when visiting anticoagulation clinics (from €6.9 to €20.5 per visit) in a multinational investigation of time and travel costs.[26]

Warfarin is also associated with a high risk of hemorrhagic complications, such as intracranial hemorrhage (ICH), in elderly patients.[12,19] In the Stroke Prevention in Atrial Fibrillation (SPAF) II study, the warfarin-treated group was noted to have a statistically significant increase in major bleeding rate and a statistically nonsignificant increase in the ICH rate. Multivariate analyses correlated warfarin-associated major bleeding with advanced age (>75 years) and greater number of prescription drugs taken.[27] In addition, supratherapeutic INR level (prothrombin time ratio >2.0, which corresponds to INR >4) was identified as the dominant independent risk factor

Warfarin is also associated with a high risk of hemorrhagic complications, such as intracranial hemorrhage, in elderly patients.

TABLE 2

$CHAD_2DS_2$-VASc Risk Score for Predicting Stroke and Thromboembolism in Patients With AF Using Novel Risk Factor-Based Approach

$CHAD_2DS_2$-VASc Risk Criteria	Score
Congestive heart failure/LV dysfunction (LVEF $\leq$ 40%)	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular Disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (female)	1
Maximum score	9

AF, atrial fibrillation; LV, left ventricle; LVEF, left ventricle ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

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for increased ICH in a case-control study of 121 patients.[28] In order to predict warfarin-associated risk of hemorrhage, a simple five-variable risk score was developed in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. The risk score consisted of presence of anemia (3 points), severe renal disease with glomerular filtration rate $<$ 30 mL/min or dialysis-dependent (3 points), age $\geq$ 75 years (2 points), prior history of bleeding (1 point), and hypertension (1 point). Based on the cumulative ATRIA score, patients could be divided into low risk (0-3 points), intermediate risk (4 points), and high risk (5-10 points), and identified as being at progressively increased risk of hemorrhage (0.8%, 2.6%, and 5.8%, respectively).[29]

It has been suggested that pharmacogenetic testing might help in deciding the appropriate dose of warfarin by individualizing therapy and thus reducing the risk of complications.[30] However, there are no randomized trials and until an appropriate path for pharmacogenetic testing and its utility for the individual patient is demonstrated to be clinically useful and cost effective, such testing remains a subject for further research evaluation.[31]

There are two groups of patients (the elderly and patients with severe renal impairment) who are at high risk of developing bleeding complications. The elderly population often has vascular disease or arthritis that requires the use of antiplatelet agents such as acetylsalicylic acid, clopidogrel, and prasugrel, or pain medication such as nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. When warfarin is taken concomitantly with antiplatelet agents and NSAIDs, there is increased risk of bleeding. Also, these patients often have polypharmacy, which increases their chance of having drug-to-drug and drug-to-food interactions and subsequently makes anticoagulation monitoring more difficult. In addition, the elderly can also have physical limitations such as gait instabilities and visual disturbances that predispose them to fall, thereby increasing the risk of bleeding. All of the issues listed above increase the bleeding risk with the therapeutic anticoagulation although the benefit of stroke prevention may outweigh the risk even in this group of patients.

The second group at higher risk of bleeding complication is patients with severe renal impairment. These patients are known to have increased thromboembolic risks (reaching a 9.8-fold increase) with AF.[32] In addition to the factors contributing to hypercoagulable state (Virchow's triad, vessel wall abnormalities, and abnormal blood constituents), hemodialysis patients also have other physiologic mechanisms that can lead to substantial changes in hemostasis, such as elevations in inflammatory and procoagulant markers.[33,34] Thus, it is essential that this group of patients be treated with therapeutic anticoagulation to prevent stroke. However, patients with severe renal impairment are also at particularly high risk of developing bleeding complications. In one systemic review of warfarin use in hemodialysis patients, it was noted that major bleeding rates ranged from 0.10 to 0.54 events per patient-years of warfarin exposure, which is twice the rate of hemodialysis patients not exposed to warfarin or subcutaneous heparin.[35] Several factors may explain the increased bleeding risk. These patients have functional abnormalities within the platelets and other pathways such as reduction in intracellular adenosine diphosphate (ADP) and serotonin, abnormal platelet arachidonic acid metabolism, defective cyclo-oxygenase activity, and altered von Willebrand factor that place them at higher bleeding risk.

In addition, these patients have other issues, such as cardiovascular disease, uncontrolled hypertension, and uremic toxins (parathyroid hormone and NSAIDs), which also contribute to elevated bleeding risk. Unfortunately, patients with severe renal impairment have often been excluded from the previous anticoagulant studies (due to the concern for increased bleeding risk), so the use of warfarin therapy in patients with severe renal impairment is controversial. Unfortunately, there are no large randomized trials that have prospectively assessed the real risk or benefit of full intensity anticoagulation in such patients. Until such data are available, it is recommended that warfarin be initiated at lower doses and monitored more closely in patients with severe renal impairment.[29]

... the use of warfarin therapy in patients with severe renal impairment is controversial.

Considering this increased risk of bleeding, the three newest anticoagulant trials have offered a lower dose of the study drug available to patients with creatinine clearance (CrCl) of 30 to 49 mL/min (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]) and serum creatinine > 1.5 mg/dL (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke [AVERROES] and Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation [ARISTOTLE]). Further subgroup analyses from these studies will help clarify the net clinical effect of these new anticoagulants in this group of high-risk patients. Because of the increased hemorrhagic risk, the risk-to-benefit ratio of therapeutic anticoagulation needs to be carefully weighed prior to initiating the treatment with anticoagulant agents in patients with significant renal impairment. In summary, warfarin is beneficial in preventing embolic stroke in AF patients; however, the issues documented above limit its use. Consequently, there is a need to search for new stroke prophylactic agents.

Antiplatelet Therapy

Antiplatelet therapy as an alternative to warfarin for stroke prophylaxis is appealing to AF patients because of its simplified treatment regimen (no need for frequent laboratory monitoring) and potentially reduced risk of bleeding complications. Acetylsalicylic acid was studied in multiple clinical trials and was noted to be less effective than warfarin in stroke prevention.[8,36] Dual antiplatelet therapy with acetylsalicylic acid and clopidogrel was later evaluated for prevention of vascular events in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) and ACTIVE A (a separate arm of ACTIVE W) trials.[37,38]

ACTIVE-W randomly assigned 6706 high-risk AF patients to either dual antiplatelet therapy (acetylsalicylic acid + clopidogrel) or warfarin for thromboprophylaxis. The dual antiplatelet group was noted to have a 44% higher rate of primary outcome (stroke, non–central nervous system systemic embolus, myocardial infarction, or vascular events; 5.6% per year vs 3.93% per year) and a 21% higher rate of total bleeding (15.4% per year vs 13.21% per year) and 23% higher rates of minor bleeding (13.58% per year vs 11.45% per year).[28] The study was terminated early due to safety reasons. The result of ACTIVE W established that dual antiplatelet therapy was inferior to warfarin and is not suitable for routine use.

The ACTIVE-A trial randomly assigned 7554 AF patients who were deemed not to be warfarin candidates to receive either dual antiplatelet therapy (acetylsalicylic acid + clopidogrel) or acetylsalicylic acid monotherapy for stroke prophylaxis. Patients who received dual antiplatelet therapy had a statistically significant 11% risk reduction in primary outcome (6.8% per year vs 7.8% per year) and 28% risk reduction in stroke (2.4% per year vs 3.3% per year). However, these patients were also noted to have a statistically significant 57% higher rate of major hemorrhagic complications (2.0% per year vs 1.3% per year) with 87% increase in intracranial bleeding (0.4% per year vs 0.2% per year) and 51% increase in extracranial bleeding (1.6% per year vs 1.1% per year).[29] Based on these data it would seem that dual antiplatelet therapy can be beneficial in reducing the risk of cardioembolic events in patients who are intolerant to warfarin.

... dual antiplatelet therapy can be beneficial in reducing the risk of cardioembolic events in patients who are intolerant to warfarin.

Results from the ACTIVE trials clearly demonstrated that oral anticoagulation with warfarin is superior to dual antiplatelet therapy in stroke prophylaxis in AF patients. Therapeutic anticoagulation with warfarin is the antithrombotic of choice for AF patients and dual antiplatelet therapy may be considered in patients who cannot tolerate or safely sustain anticoagulation with warfarin.[39] Because of the increased bleeding risk, the combination therapy with

acetylsalicylic acid and clopidogrel as antiplatelet agent for secondary prevention of stroke and TIA has been given a class III recommendation unless patients have a specific indication for the dual antiplatelet therapy (eg, coronary stent or acute coronary syndrome) in the recent update to the American Heart Association (AHA)/American Stroke Association recommendations for the prevention of stroke in patients with stroke and transient ischemic attack.[40]

Oral Anticoagulants: New and Emerging Treatment Strategies

Because of the limited efficacy of dual antiplatelet therapy and the problems associated with warfarin, there has been an ongoing search for newer oral anticoagulants for stroke prevention. These efforts led to the development of direct thrombin inhibitors (DTIs), direct and indirect factor Xa (FXa) inhibitors, and other warfarin antagonists. In general, these agents have more rapid onset of action, fewer food and drug interactions, and more predictable anticoagulation response (Figure 3, Table 3).

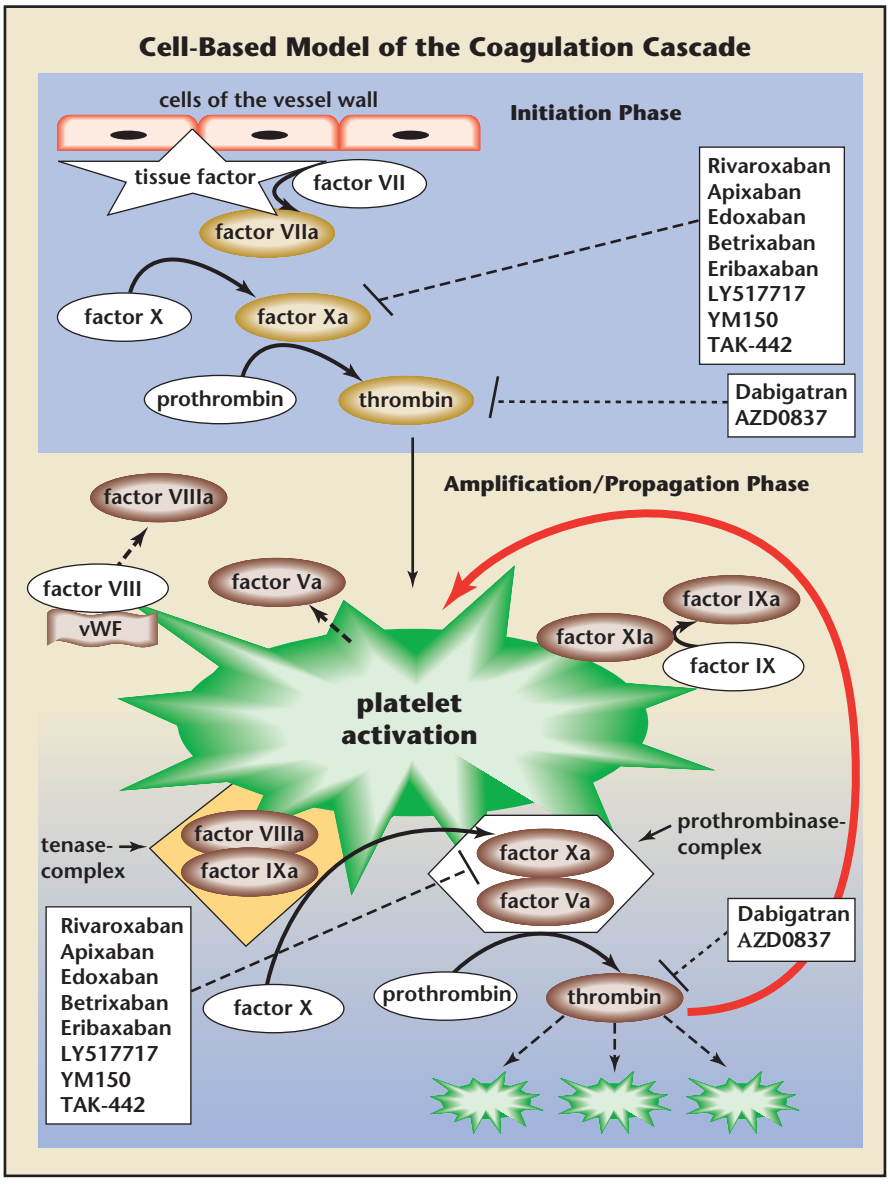

Figure 3. Mechanisms of action for new anticoagulants. Reproduced with permission from Ahrens I et al.[42]

DTIs

Dabigatran is a new oral DTI that has been extensively studied and recently approved by the US Food and Drug Administration (FDA) for stroke prevention in nonvalvular AF patients (Table 3).[4,41] Dabigatran etexilate is rapidly converted to dabigatran and is absorbed in acidic environments.[42-44] It has a rapid onset of action and can be conveniently taken at a daily fixed dose without coagulation monitoring. It is excreted renally so the dosage needs to be adjusted in patients with severe renal impairment (CrCl $<$30 mL/min). Unlike warfarin, its metabolism does not require CYP450 systems and it does not have significant drug-to-drug or drug-to-food interactions that are related to this enzyme system (Table 3). It is also a substrate for P-glycoprotein (Pgp) and its plasma drug level can be affected by Pgp inducers or inhibitors. The concomitant use of dabigatran and rifampin (a Pgp inducer) can reduce the dabigatran level (exposure) and the manufacturer has recommended avoiding the combination of dabigatran and rifampin.[45] Also, dronedarone (an antiarrhythmic agent commonly used in AF patients) is a Pgp inhibitor; as such it can increase the dabigatran level by 1.7- to 2.0-fold, thereby increasing the bleeding risk when used together.[36,46] Based on the reports and concerns about the interaction between dronedarone and dabigatran, there has been a recent update regarding dabigatran use concomitant with dronedarone in patients with moderate renal insufficiency (CrCl $<$50 mL/min), suggesting that clinicians should consider using the lower dose of dabigatran (75 mg twice daily) in such patients. Furthermore, this advisory further

TABLE 3

Warfarin Interactions With Drugs, Natural Health Products, and Food

Drug Products	
Antibiotics	Most agents (macrolides, fluoroquinolones, metronidazole, clo-trimoxazole, rifampin)
Antifungals	Fluconazole, miconazole, itraconazole
Antidepressants	SSRI: fluoxetine, paroxetine, sertraline
Nonsteroidal anti-inflammatory agents	Acetylsalicyclic acid, celecoxib
Stomach ulcer/acid-reducing agents	Cimetidine, omeprazole, ranitidine
Lipid-lowering agents	Fibrates, statin such as lovastatin and simvastatin
Natural Health Products	
Chondroitin plus glucosamine	Ginseng
Coenzyme Q10	Green tea
Dashen	Horse chestnut
Devil's claw	*Lycium barbarum*
Dong quai (*Angelica sinensis*)	Papaya extract
Feverfew	St. John's wort
Fenugreek together with boldo	Vitamin A
Fish oil supplements with EPA and DHA	Vitamin K
Gingko biloba	Wintergreen
Food	
Avocado	Mango
Cranberry juice	Onions
Flax (flaxseed)	Papaya
Garlic	Seaweed (sushi wrap)
Ginger	Soy protein products (including soymilk and tofu)

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SSRI, selective serotonin reuptake inhibitor.
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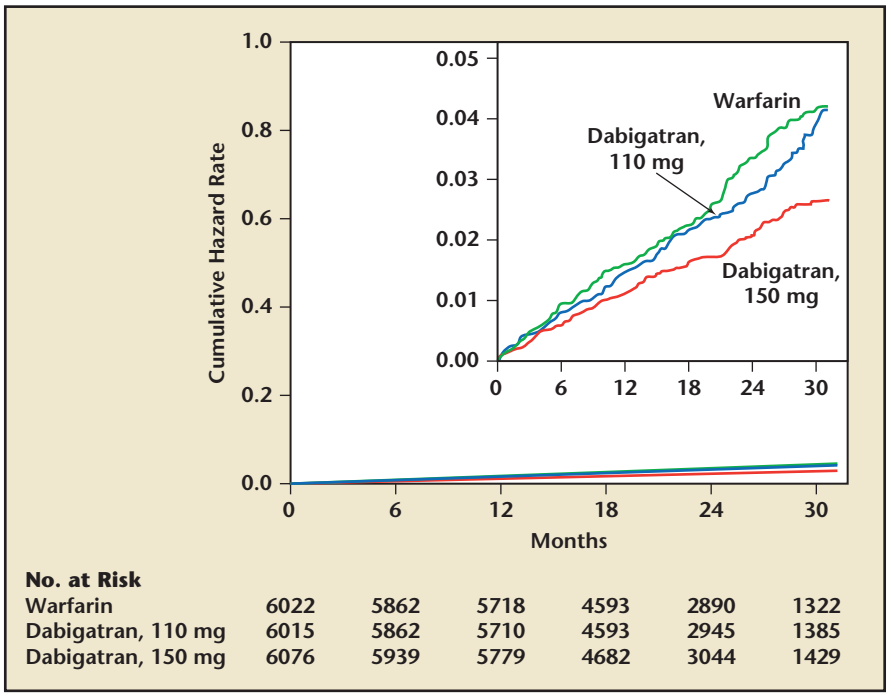
emphasizes that the concomitant use of dabigatran and Pgp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.[47] In addition, when dabigatran is taken concomitantly with other Pgp inhibitors (amiodarone, clarithromycin, cyclosporine, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, tacrolimus, and verapamil), the plasma drug level may be higher than the baseline level, which can increase bleeding risk as well.[48,49] Because of these potential drug interactions, clinicians need to adjust the dabigatran dose whenever a Pgp inhibitor is added or withdrawn from therapy and should carefully monitor for bleeding complications during their concomitant use.[39]

Dabigatran was studied in the Dabigatran With or Without Concomitant Aspirin Compared With Warfarin Alone in Patients With Nonvalvular Atrial Fibrillation (PETRO) study and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study. Results from the PETRO study showed that dabigatran, 150 mg twice daily and 300 mg twice daily, was beneficial in preventing thromboembolic events. However, there was higher bleeding risk in the 300 mg twice daily plus acetylsalicylic acid group. The medication was well tolerated with the exception of some gastrointestinal symptoms (diarrhea, nausea, and vomiting), and it did not cause any significant liver transaminase elevation.[50]

The RE-LY study was a multicenter, randomized, open-labelstudy that compared dabigatran etexilate with dose-adjusted warfarin



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 4. Cumulative hazard rate for primary outcome of stroke or systemic embolism based on treatment group. From *The New England Journal of Medicine*, Connolly SJ et al, "Dabigatran versus Wafarin in Patients with Atrial Fibrillation," Volume 361, pages 1139-1151, Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[51]

in 18,113 AF patients. Dabigatran, 150 mg twice daily (D150), was superior to warfarin and dabigatran, 110 mg twice daily (D110), was noninferior to warfarin in the primary outcome of stroke and systemic embolism (Figure 4). Both doses of dabigatran had lower risks of bleeding, including major bleeding, life-threatening bleeding, intracranial bleeding, and major or minor bleeding, and a higher risk of major gastrointestinal bleeding, whereas the warfarin group actually had higher incidence of hemorrhagic stroke. Dyspepsia was more common with dabigatran secondary to the tartaric acid coating of the medication.[51]

In summary, high-dose dabigatran (D150) had superior antithrombotic efficacy leading to a 35% relative reduction of stroke and systemic embolization compared with warfarin, whereas the low-dose dabigatran (D110) had similar antithrombotic efficacy to warfarin in stroke prevention. Findings from the RE-LY study suggested that dabigatran is safe and is a potential alternative to warfarin. The FDA approved dabigatran for the prevention of stroke and systemic embolism in nonvalvular AF patients (150 mg twice daily for patients with normal renal function and 75 mg twice daily for patients with renal impairment). In addition, the American College of Cardiology (ACC)/AHA practice guideline was recently updated to include dabigatran as first-line option for anticoagulation in high-risk AF patients.[52] The option of changing from dose-adjusted warfarin to fixed-dose dabigatran is good news to clinicians and patients, especially with its enhanced efficacy, reduction of bleeding, and no need to monitor anticoagulation. It will likely help achieve therapeutic anticoagulation in a greater number of AF patients, as well as improve long-term compliance due to its ease of use.

The option of changing from dose-adjusted warfarin to fixed-dose dabigatran is good news to clinicians and patients.

Since its FDA approval, dabigatran has been extensively used by clinicians around the world. However, recently there has been significant concern due to reports of increased bleeding events in patients taking dabigatran. The manufacturer has also reported 260 fatal bleeding events in patients taking dabigatran after the postmarketing database was evaluated. These findings have prompted labeling updates in Europe and the United States as well as safety advisories issued in Japan and Australia.[53] This has also prompted an FDA investigation to determine whether the reports of bleeding in patients taking dabigatran are occurring more commonly than would be expected based on observations in the clinical trial that supported its approval.[53] An extension of the RE-LY study, the RELY-ABLE Long Term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed RE-LY Trial (RELY-ABLE) study, is actively ongoing to evaluate the long-term safety effect of dabigatran.

FXa Inhibitors

FXa is a protease situated at the convergence of the extrinsic and intrinsic pathways in the coagulation cascade. It is responsible for the amplification of thrombin generation, which leads to thrombus formation.[38] Direct FXa inhibitors inactivate both prothrombinase-bound FXa and free FXa, and indirect FXa inhibitors interact with antithrombin to exert their anticoagulant effect (Figure 3).[18,20]

Rivaroxaban is one of the direct FXa inhibitors that has been evaluated as an antithrombotic agent

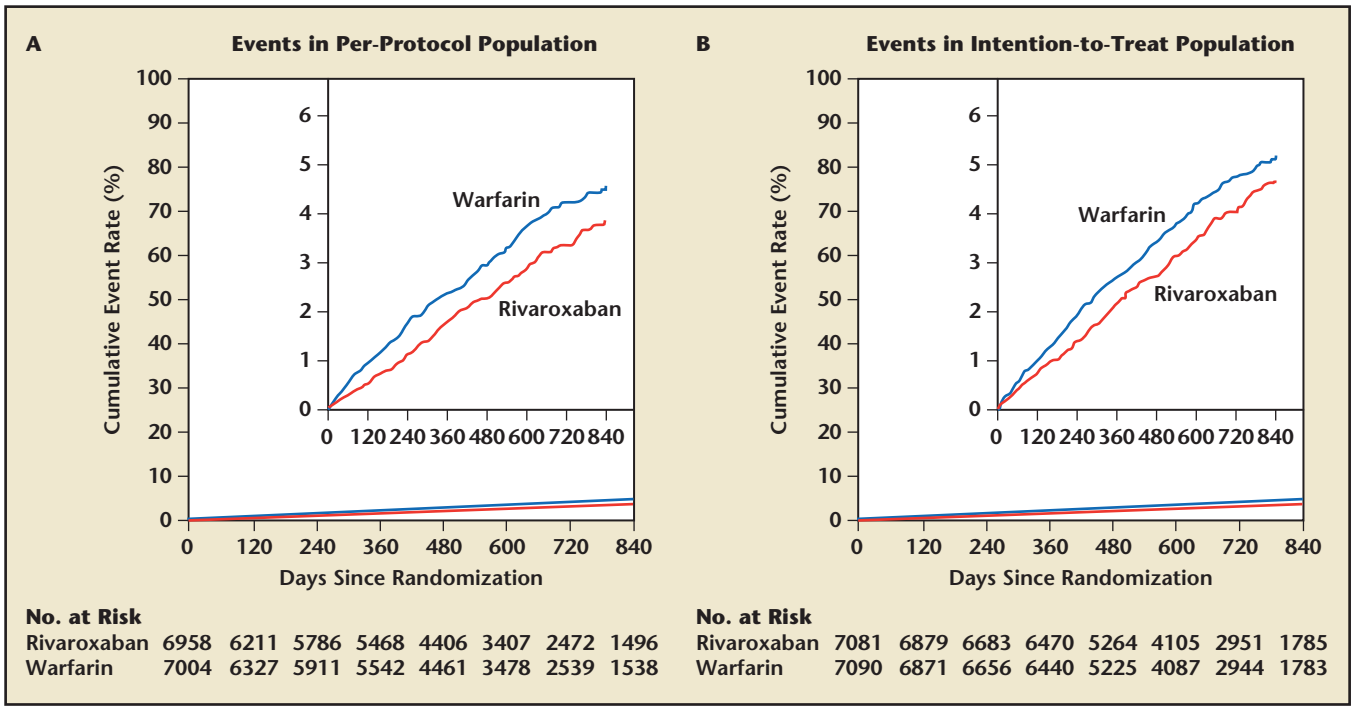


Figure 5. Cumulative rates of the primary endpoint (stroke or systemic embolism) in the per-protocol and in the intention-to-treat population. From *The New England Journal of Medicine*, Patel MR et al, "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation," Volume 365, Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[56,57]

for AF management and recently received the treatment indication from the FDA for AF (Table 3). It has a rapid onset of action with high oral bioavailability (Table 3). It is metabolized by the CYP450 system two-thirds of the time and is excreted unchanged the other one-third of the time. Similar to dabigatran, it is also a substrate for the Pgp. The plasma drug concentration can increase when rivaroxaban is coadministered with CYP3A4 and Pgp inhibitors such as azole-antimycotics and human immunodeficiency virus-protease inhibitors.[49] This is in contrast to dabigatran, which does not have any significant interaction with CYP450-dependent drugs. Moreover, the plasma drug concentration can increase in those patients with renal insufficiency. Therefore, rivaroxaban is not recommended for patients with CrCl $<$15 mL/min and it needs to be used with caution in patients with severe renal impairment (CrCl 15-29 mL/min).[54] Rivaroxaban was evaluated as an antithrombotic agent for AF patients in the ROCKET-AF trial.[55,56] It was found to be noninferior to warfarin in preventing stroke and systemic embolism when analyzed by the intention to treat principle (hazard ratio [HR] 0.88; $P = .12$) (Figure 5). The rivaroxaban-treated group also had less intracranial bleeding (HR 0.67; $P = .02$) but more bleeding from gastrointestinal sites (3.2% vs 2.2%; $P < .001$) (Table 5). Moreover, the primary efficacy outcome was independent of each center's INR control (HR 0.70-0.89). As can be predicted, the adverse event rate for the warfarin group was highest in the center with the lowest median time in TTR (2.53 per 100 patient-years) and lowest in the center with highest median TTR (1.80 per 100 patient-years).[57,58] At the end of the study, 92.2% of the patients in both study groups were transitioned to warfarin for stroke prevention. Median time to reach therapeutic INR was 13 days for those patients who were previously taking rivaroxaban and 3 days for those patients who were taking warfarin. Results showed that patients in the rivaroxaban group had more primary events during the first month after the termination of the study (22 vs 7; $P = .008$). One reason that may explain the finding is that patients in the rivaroxaban group did not receive dual anticoagulation during the transition period secondary to concern for increased bleeding risk. The lack of dual anticoagulation might have placed these patients at subtherapeutic anticoagulation for an extended period of time, which placed them at greater risk of embolic complications.

These data suggest that rivaroxaban is another alternative to warfarin for AF patients with moderate or high risk for thromboembolic events and requires once-daily dosing. It should be noted that, although rivaroxaban has been approved for clinical use with a once-daily dosing regimen, its half-life is only 7 to 11 hours. There was extensive discussion during the FDA review and the advisory

committee thought that the drug is best suited at twice-daily dosing because of its pharmacokinetics. However, as the approval was primarily based on the data from the ROCKET-AF trial (where it was used once a day), there was no other choice except approval in the once-daily dosing format. Future studies should consider comparing the efficacy of once-daily versus twice-daily dosing.

Apixaban is another selective reversible oral direct FXa inhibitor that has been extensively studied for prevention of venous thromboembolism (VTE) and stroke. It has a rapid onset of action and is metabolized through kidney, liver (CYP450), and intestine (Table 3).[18,38] Apixaban was evaluated in a double-blinded, randomized, multicenter, phase III AVERROES trial as a stroke prophylactic agent. This trial included 5599 AF patients (mean $CHADS_2$ score of 2) who had at least one risk factor for stroke and who were also ineligible for warfarin treatment or who had not tolerated previous warfarin treatment. These patients were randomly assigned to either acetylsalicylic acid (81 to 324 mg) or apixaban (5 mg twice daily or 2.5 mg twice daily in those patients who met two of the following criteria: age $\geq$ 80 years, weight $\leq$ 60 kg, serum creatinine concentration $\geq$ 1.5 mg/dL). Patients who were treated with apixaban had statistically and clinically significant reduction in stroke and systemic embolic rates without significantly increased risk of major bleeding (HR 1.13; $P = .57$) or intracranial bleeding (HR 0.85; $P = .69$). Specifically, apixaban lowered mortality by 21% and reduced thromboembolic events by 55% when compared with acetylsalicylic acid. Because of the favorable outcome, the study was terminated early by the data and safety monitoring board.[59,60]

Apixaban was compared with warfarin in AF patients with at least one risk factor for stroke in the ARISTOTLE trial.[61] This trial enrolled 18,201 AF patients (mean $CHADS_2$ score of 2.1) in 1034 centers over 39 countries. These patients were randomly assigned to either apixaban (5 mg twice daily or 2.5 mg twice daily in those patients who met two of the following criteria: age $\geq$ 80 years, weight $\leq$ 60 kg, serum creatinine concentration $\geq$ 1.5 mg/dL) or warfarin (target INR 2.0-3.0). The primary objective was to evaluate the combined endpoints of stroke, systemic embolism, and all-cause mortality. The apixaban group had a significantly lower rate of the primary outcome (HR 0.79; $P < .001$ for noninferiority; $P = .01$ for superiority) (Table 4). The apixaban group was also superior in safety. Patients in the apixaban group had a significantly lower rate of major bleeding (HR 0.69; $P < .001$), lower rate of hemorrhagic stroke (HR 0.51; $P < .001$), lower rate of death from any cause, and lower rate of intracranial bleeding (HR 0.42; $P < .001$). In addition, the apixaban group also had a reduced rate of gastrointestinal bleeding in contrast to the other oral direct FXa inhibitor, rivaroxaban, as well as the DTI, dabigatran.[62] These data suggest that of the available newer antithrombotic agents apixaban has the best safety and efficacy profile and appears to be a suitable and perhaps better alternative to warfarin for AF patients.

Edoxaban is another oral direct FXa inhibitor that has been studied in AF patients in the phase II trials (Table 3). Once-daily dosing regimens (30 mg and 60 mg) are safe and well tolerated but twice-daily dosing regimens (30 mg and 60 mg) caused significant increase in the bleeding events.[63] Currently, edoxaban is being compared with warfarin in high-risk AF patients in the Evaluation of Efficacy and Safety of DU-176b Versus Warfarin In Subjects With Atrial Fibrillation — Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction (ENGAGE AF-TIMI) trial. The primary outcome includes stroke and systemic embolic events and secondary endpoints consist of composite clinical outcome of stroke, systemic embolic events, all-cause mortality, and major bleeding events.[64] Another FXa inhibitor under development is betrixaban and the initial results from the pilot study (EXPLORE-Xa study: Phase 2 Study of the Safety, Tolerability and Pilot Efficacy of Oral Factor Xa Inhibitor Betrixaban Compared to Warfarin) presented at the ACC meeting showed an increasing risk of bleeding with higher doses of this agent.[38,65] The precise role of betrixaban in AF remains to be evaluated.

Indirect Factor Xa Inhibitors

Indirect FXa inhibitors have also been developed and studied as potential therapy for deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment, as well as for stroke prophylaxis in AF patients (Table 3). Idraparinux is antithrombin-dependent specific inhibitor of FXa with a rapid onset of action (Figure 3). It has a long half-life and can be given as a weekly subcutaneous injection.[32] Idraparinux was evaluated in the AF patients in the Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in

Indirect FXa inhibitors have also been developed and studied as potential therapy for deep vein thrombosis and pulmonary embolism treatment, as well as for stroke prophylaxis in AF patients.

TABLE 4

Anticoagulant Properties

Substance	Mechanism of Action	Half-Life (h)	Peak Plasma Volume (h)	Metabolism/Excretion	Recent AF Research Study
Factor IIa Inhibitors (Thrombin)					
Dabigatran etexilate	Competitive binding of F IIa	14-17	0.5-2	Renal, 80% unchanged in urine	PETRO, RE-LY, RE-LY ABLE
Direct Factor Xa Inhibitors					
Rivaroxaban	Competitive binding of FXa	7-11	2-3	Renal (1/3), liver (2/3 cytochrome p450)	Rocket-AF
Apixaban	Competitive binding of FXa	8-14	3	Renal, liver (cytochrome P450), intestinal	ARISTOTLE, AVERROES
Betrixaban	Competitive binding of FXa	~ 20		Bile with minimal renal excretion	EXPLORE-Xa
Edoxaban	Competitive binding of FXa	9-11	1-2	Renal	ENGAGE TIMI-48
Indirect Factor Xa Inhibitors					
Idraparinux	Indirect Factor Xa Inhibitor	130	2.5		AMADEUS, Borealis-AF
Biotinylated-Idraparinux	Indirect Factor Xa Inhibitor				
Vitamin K Antagonists (VKA)					
Tecarfarin	Inhibit synthesis of vitamin-K dependent clotting factors	119		Hepatic (noncytochrome P450 medicated)	Embrace AC

AF, atrial fibrillation.

Data from Turpie AG,[41] Weitz JI,[22] Ahrens I et al,[42] and Sobieraj-Teague M et al, "New Anticoagulants for Atrial Fibrillation," *Semin Thromb Hemost.* 2009;35:515-524.

TABLE 5

Results of the ROCKET-AF Trial

Primary Efficacy Outcome	Rivaroxaban Event Rate	Warfarin Event Rate	HR	95% CI	*P* Value Noninferiority
Event Rate (per 100 patient-years)					
Per protocol, as treated	1.7	2.2	0.79	0.66–0.96	< 0.001
Intention to treat	2.1	2.4	0.88	0.75–1.03	< 0.001
Secondary Efficacy Outcome					
Event Rate (per 100 patient-years)					
Vascular death, stroke, embolism	3.11	3.63	0.86	0.74–0.99	0.034
Hemorrhagic stroke	0.26	0.44	0.59	0.37–0.93	0.024
Non-CNS embolism	0.04	0.19	0.23	0.09–0.61	0.003
All-cause mortality	1.87	2.21	0.85	0.70–1.02	0.073
Primary Safety Outcome					
Event Rate (per 100 patient-years)					
Major and nonmajor clinically relevant bleeding	14.9	14.5	1.04	0.96–1.11	0.44
Major bleeding	3.6	3.4	1.04	0.90–1.20	0.58
> 2 g/dL Hgb drop	2.8	2.3	1.22	1.03–1.44	0.02
Transfusion (> 2 units)	1.6	1.3	1.25	1.01–1.55	0.04
Critical organ bleeding	0.8	1.2	0.69	0.53–0.91	0.007
Intracranial bleeding	0.5	0.7	0.67	0.47–0.93	0.02
Bleeding causing death	0.2	0.5	0.50	0.31–0.79	0.003

Primary efficacy outcome measured stroke or non–central nervous system embolism.
CI, confidence interval; CNS, central nervous system; Hgb, hemoglobin; HR, hazard ratio.
Data from Patel MR et al.[56,57]

Patients With Atrial Fibrillation (AMADEUS) trial. Although the results demonstrated that idraparinux was as effective as warfarin in thromboprophylaxis, the trial was stopped prematurely due to increased bleeding risk.[66] Because of the disappointing finding from the AMADEUS trial, no additional studies have been planned at the current time for AF patients.

Idrabiotaparinux (a biotinylated idraparinux) is another indirect FXa inhibitor currently being evaluated in patients with DVT, PE, and AF (Figure 3, Table 3). Its antithrombotic effect is reversible with avidin, which is unique among these newly developed anticoagulants. It is being investigated in AF patients with $CHADS_2$ scores ≥ 2 in the Evaluation of Weekly Subcutaneous Biotinylated Idraparinux Versus Oral Adjusted-dose Warfarin to Prevent Stroke and Systemic Thromboembolic Events in Patients With Atrial Fibrillation (Borealis-AF) trial.[18] Further studies are still needed to help establish the role of idrabiotaparinux in stroke prevention in AF patients.

New Vitamin K Antagonists

Tecarfarin is a selective oral vitamin K epoxide reductase enzyme inhibitor with a terminal half-life of 119 hours (Table 3). It is metabolized by carboxylesterases instead of the CYP450 system (Figure 3). Its safety and tolerability were examined in 66 AF patients with mild to moderate risk of stroke (phase II trial). Available data revealed that a therapeutic drug level was achieved 71.4% of the time and extreme supratherapeutic (INR >4.0) or extreme subtherapeutic levels (INR <1.5) were found only 1.2% of the time.[67] Based on these findings, investigators concluded that tecarfarin may be a safer and more reliable vitamin K antagonist. They did urge that additional prospective trials with adequate powers are needed.[67] At the current time, tecarfarin is being studied in 600 patients with either AF, atrial flutter, prosthetic heart valves, VTE, or a history of myocardial infarction or cardiomyopathy in a phase II/III trial. Results of this new trial will help define the role of tecarfarin in these clinical settings.

Cost Effectiveness of New Anticoagulants

Newly developed and studied antithrombotic agents such as dabigatran, rivaroxaban, and apixaban are promising stroke prophylactic agents for AF patients. A recent article evaluated the cost effectiveness of dabigatran for ischemic stroke prevention in nonvalvular AF patients who were age $\geq$ 65 years. Researchers evaluated quality-adjusted survival, costs, and cost effectiveness of dabigatran compared with adjusted-dose warfarin based on the drug cost in Europe. Data showed that high-dose dabigatran was the most effective treatment option when compared with warfarin and suggested that dabigatran may be a cost-effective alternative to warfarin in nonvalvular AF patients with increased risk of stroke.[68] The recently announced price of dabigatran in the United States is considerably lower than it is in Europe (approximately $210 per month); therefore, it seems reasonable to think that overall dabigatran use will be cost effective.

Conclusions

AF is the most common sustained cardiac arrhythmia and is a major cause of embolic stroke. Although until recently warfarin therapy had been the only effective therapy for stroke prophylaxis, its clinical use had been limited due to a narrow therapeutic window, multiple drug and food interactions, the need for frequent monitoring and adjustment, and concern for bleeding. Because of these issues, warfarin has been either underutilized in at-risk patients or is subtherapeutic in prescribed patients, and subsequently exposes them to embolic strokes.

The recent development of newer antithrombotic agents such as DTIs and FXa inhibitors now provides us with several suitable alternatives to warfarin. These newer anticoagulants have characteristics that make them more appealing to clinicians and patients. However, there is concern due to the lack of a suitable antidote to reverse the anticoagulant action of many of these newer agents. Despite this shortcoming, these newer drugs do offer a viable alternative to warfarin in AF patients with a moderate to high risk of developing cardioembolic complications. Results from numerous ongoing studies will provide critical information needed to better define the role of these new oral anticoagulants in different clinical settings. ■

Newly developed and studied antithrombotic agents such as dabigatran, rivaroxaban, and apixaban are promising stroke prophylactic agents for AF patients.

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MAIN POINTS

- Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is especially prevalent in the elderly population. AF is associated with many complications, including cardioembolic strokes. Pharmacologic antithrombotic strategies, including antiplatelet agents and oral anticoagulants, have been used to prevent cardioembolic complications.
- Patients are treated with oral anticoagulation using warfarin or aspirin based on their cardioembolic stroke risk. Although warfarin has been the only effective therapy, it is underutilized clinically due to drug-to-drug and food-to-drug interactions and hemorrhagic complications.
- Dual antiplatelet therapy with aspirin and clopidogrel has been studied as a potential alternative anticoagulant for AF patients; however, the combination of aspirin and clopidogrel was noted to be inferior to warfarin in preventing strokes.
- Newer anticoagulants agents, including direct thrombin inhibitors, direct and indirect factor Xa inhibitors, and vitamin K antagonists, have been developed and evaluated in AF patients.
- These new agents have been proven to be as effective as warfarin and easier to use because of lack of drug-to-drug and food-to-drug interactions as well as no need to monitor International Normalized Ratio.

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