Novel anticoagulants in atrial fibrillation stroke prevention

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Abstract: This review article evaluates novel oral anticoagulants in comparison with warfarin for thromboembolism prophylaxis in patients with atrial fibrillation (AF). AF is the most frequently diagnosed arrhythmia in the United States. The most serious side effect of AF is stroke. Warfarin has several decades of proven efficacy in AF-related stroke prevention but the drug's numerous drawbacks make its implementation difficult for practitioners and patients. The difficulties of warfarin have prompted the development of alternative anticoagulants for AF-related stroke prevention with better efficacy, safety, and convenience. The oral direct thrombin inhibitor, dabigatran, and the oral factor Xa inhibitors, rivaroxaban and apixaban, have been evaluated in a large phase III trial. Dabigatran, rivaroxaban and apixaban were shown to be noninferior compared with warfarin in the prevention of stroke. Dabigatran and apixaban were found to be statistically superior to warfarin. All three may also have a better safety profile than warfarin. In conclusion, novel anticoagulants have a different pharmacologic profile compared with warfarin that may eliminate many of the treatment inconveniences. Practitioners must also be aware of the disadvantages these new drugs possess when choosing a management strategy for their patients. Drug selection may become clearer as these new drugs are used more extensively.

Keywords: anticoagulation, apixaban, dabigatran, rivaroxaban, thromboembolism, warfarin

Introduction

Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia, affecting over 2.2 million people in the United States: close to 1% of the total population. Its prevalence increases with age with as many as 10% of people older than 80 years affected. It is estimated that the number of people diagnosed with AF will approach nearly 16 million in the United States by 2050 [Miyasaka *et al.* 2006].

AF is characterized by a lack of coordinated electrical and mechanical atrial activity that promotes intra-atrial thrombus formation, primarily in the left atrial appendage. Fragments from these thrombi can then dislodge and travel to the brain to cause a stroke. The risk of stroke is increased approximately fivefold in patients with AF [Roger *et al.* 2011]. Up to 15% of all strokes are due to AF and strokes in those with AF are more severe and have worse outcomes than strokes in those without AF [Wolf *et al.* 1991; Lin *et al.* 1996; Marini *et al.* 2005]. The mortality rate in people with AF is twice that of age-matched individuals with a normal heart rhythm driven, at least in part, by this increase risk of stroke [Lin *et al.* 1996]. In addition, strokes associated with AF have a significant impact on quality of life and add significantly to the economic burden of the disease [Friberg *et al.* 2003; Marini *et al.* 2005; Roger *et al.* 2011].

For many decades, aspirin and warfarin have been the only approved antithrombotic therapies for stroke prevention in patients with AF. Aspirin has been shown to be superior to placebo in preventing AF-related strokes [Aguilar and Hart, 2005]. However, aspirin alone or when used together with clopidogrel is less effective than warfarin and is therefore currently recommended when risk of stroke is low or when patients with AF cannot or will not take warfarin [Connolly *et al.* 2006; Mant *et al.* 2007; Wann *et al.* 2011]. Warfarin has been proven to be highly effective in preventing

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AF-related strokes and is recommended in patients with a $CHADS_2$ score (a prediction score based on whether a person is 75 years or older, has heart failure, hypertension, diabetes mellitus, and/or a prior stroke or transient ischemic attack [TIA]; the higher the score, the greater the risk) of 2 or higher [Gage *et al.* 2001; Hart *et al.* 2007; Singer *et al.* 2008]. However, because of the difficulty in its management, a large proportion of AF patients eligible for warfarin do not receive it or receive an inadequate dose [Friberg *et al.* 2003; Go *et al.* 2003; Fang *et al.* 2004; Gladstone *et al.* 2009]. Warfarin has a narrow therapeutic window and requires frequent monitoring to reduce thrombosis risk while limiting bleeding risk. Management of warfarin is complicated by numerous food and drug interactions. Maintaining a therapeutic range has proven difficult as a significant number of patients' INRs (international normalized ratios) deviate from target range resulting in an increased risk for either thromboembolism or hemorrhage [Matchar *et al.* 2002; Connolly *et al.* 2006; Gladstone *et al.* 2009]. The difficulties of warfarin have prompted the development of alternative anticoagulants for AF-related stroke prevention with better efficacy, safety, and convenience. Prospective warfarin replacements include direct thrombin inhibitors and factor Xa (FXa) inhibitors. In this review we focus primarily on the novel anticoagulants that have finished a phase III trial: dabigatran, rivaroxaban, and apixaban.

Warfarin

The efficacy of warfarin in the prevention of stroke and systemic embolization in patients with atrial fibrillation has been studied in numerous trials [Petersen *et al.* 1989; The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990; Stroke Prevention in Atrial Fibrillation Study Investigators, 1991; Connolly *et al.* 1991; Ezekowitz *et al.* 1992; Stroke Prevention in Atrial Fibrillation II Study Investigators, 1994]. Warfarin is a vitamin K antagonist that causes the synthesis of biologically inactive forms of clotting factors II, VII, IX and X. As the functional forms of these clotting factors degrade the anticoagulant effect becomes apparent. The peak effect of warfarin is dependent on the clearance of factor II (plasma half-life of 60 hours or longer) and may not occur for 2–7 days following initiation of therapy [O'reilly and Aggeler, 1968]. During the initial stages of warfarin dosing, a thrombogenic effect can occur from the depletion of naturally occurring anticoagulants protein C and protein S. Owing to its slow onset and early procoagulant effect, higher-risk AF patients may need a parenteral anticoagulant during the initiation or interruptions of therapy to bridge the patient until warfarin reaches peak effect [Singer *et al.* 2008]. The pharmacodynamic effects of warfarin are measured using the INR. An INR between 2.0 and 3.0 has been generally recommended to balance safety and efficacy for most patients with AF who receive warfarin anticoagulation. The lack of appropriate monitoring may lead to a significant amount of warfarin-related adverse events [Gurwitz *et al.* 2007]. Monitoring of INR and dose adjustments of warfarin are frequently required. Daily monitoring is needed initially and monthly monitoring is needed after a steady state has been established [Singer *et al.* 2008]. Strict INR control is important to improve patient outcome [The European Atrial Fibrillation Trial Study Group, 1995; Jones *et al.* 2005; White *et al.* 2007], but is difficult to achieve. A large and increasing number of drugs interact with warfarin leading to over-anticoagulation, under-anticoagulation, or increased bleeding [Holbrook *et al.* 2005; Juurlink, 2007]. Differences in the dietary content of vitamin K are known to profoundly alter the pharmacodynamic effects of warfarin [Franco *et al.* 2004; Khan *et al.* 2004; Kurnik *et al.* 2004; Schurgers *et al.* 2004; Couris *et al.* 2006; Rohde *et al.* 2007; De Assis *et al.* 2009]. Warfarin is extensively metabolized in the liver by the cytochrome P-450 2C9 (CYP2C9) isoenzyme. Possession of a variant allele (CYP2C9*2 and CYP2C9*3) greatly reduces warfarin metabolism and is associated with an increased risk of over-anticoagulation and of bleeding events [Aithal *et al.* 1999; Taube *et al.* 2000; Leung *et al.* 2001; Higashi *et al.* 2002; Meckley *et al.* 2008]. Polymorphisms in the gene coding for the vitamin K epoxide reductase complex 1 (VKORC1), the target protein for warfarin, leads to a protein that is either sensitive or resistant to warfarin inhibition. It is estimated that genetic alterations in CYP2C9 and VKORC1 together with age and body size could explain as much as 63% of warfarin dose variability [Herman *et al.* 2006; Vecsler *et al.* 2006].

Warfarin is among the top 10 drugs with the largest number of serious adverse event reports submitted to the United States Food and Drug Administration (FDA) during last 20 years. The major safety concern of warfarin is the risk of major bleeding. Major bleeding from warfarin

Table 1. Pharmacokinetics of novel anticoagulants.

	Rivaroxaban [Weinz *et al.* 2009]	Dabigatran [Blech *et al.* 2008]	Apixaban [Raghavan *et al.* 2009]
Dosing	20 mg daily	150 mg twice daily	5 mg twice daily
Bioavailability	66% (20 mg dose)	6–7%	50–85%
Volume of distribution	~501	60–701	16–251
Half-life	5–9 h (<45 years old); 11–13 h (>60 years old)	12–17 h; renal impairment, 15–34.1 h	12–15 h
Onset of maximal effect	2–4 h	1–2 h	1–3 h
Offset of pharmacodynamic effect	24–48 h	Parallels elimination half-life	Parallels elimination half-life
Route of elimination	66% renal secretion (36% unchanged drug); hepatic metabolism: 32% via CYP3A4/5 (primary) and CYP2J2, 14% via non-CYP hydrolysis	80% renal excretion; minimal hepatic metabolism	25% renal excretion; 55% via fecal route; hepatic metabolism via CYP3A4/3A5
Potential drug interactions	Potent CYP3A4 inhibitors and P-gp inhibitors*	Potent P-gp inhibitors*	Potent CYP3A4 inhibitors*

*Strong inhibitors of both CYP3A4 and P-gp include ketoconazole, itraconazole, voriconazole, and ritonavir. Potent CYP3A4 inhibitors include ketoconazole, macrolides (e.g. clarithromycin), verapamil and protease inhibitors (e.g. atanazavir). CYP, cytochrome P450 enzyme; P-gp, P-glycoprotein.

can lead to hospitalization, transfusion, surgery, or death. Intracranial bleeding is the most serious bleeding complication with warfarin because of the likelihood of mortality or subsequent disability.

Direct thrombin inhibitors: dabigatran

Dabigatran, in active form, is a competitive direct thrombin inhibitor that inhibits thrombin-dependent conversion of fibrinogen to fibrin and thrombin-induced platelet aggregation [Stangier *et al.* 2007, 2008; Blech *et al.* 2008]. It is highly selective, binding reversibly to fibrin-bound, clot-bound, and free thrombin with high affinity. Dabigatran is not absorbed via the oral route. Dabigatran etexilate, which does not exhibit any anticoagulant activity, is an orally bioavailable prodrug that is rapidly converted by esterase-catalyzed hydrolysis to its active form, dabigatran. The prodrug has a poor oral bioavailability (Table 1), but nevertheless yields predictable, reproducible, and therapeutically sufficient concentrations of dabigatran. The oral bioavailability may increase by up to 75% when pellets are taken out of the hydroxypropylmethylcellulose (HPMC) capsule. Therefore, capsules should not be opened and pellets taken alone.

The peak plasma concentrations and anticoagulant effects of dabigatran occur rapidly after oral administration (~2 h) and reaches steady state in approximately 3 days after twice-daily dosing [Liesenfeld *et al.* 2006]. Dabigatran prolongs the activated partial thromboplastin time (aPTT), however drug concentration and aPTT are not linearly related, which limits the tests sensitivity. In patients who bleed or thrombose while on dabigatran, aPTT may be useful in identifying undesirable anticoagulant activity. When available, thrombin time and ecarin clotting time may be more sensitive tests to evaluate the anticoagulant effects of dabigatran. Prothrombin time and INR are prolonged by dabigatran but do not correlate well with dabigatran levels. Thus, prothrombin time and INR are not appropriate to assess dabigatran anticoagulant effects [Eriksson *et al.* 2008].

The anticoagulant effects of dabigatran decline in parallel with declining plasma concentrations of the drug [Stangier, 2008]. It is predominantly excreted via the renal pathway as unchanged drug

Table 2. Study populations from phase III trials.

	RE-LY	ROCKET	ARISTOTLE
Comparator	Warfarin	Warfarin	Warfarin
N	18,113	14,264	18,201
Age	72	73	70
Prior stroke	20%	55%	19%
HTN	79%	91%	87%
HF	32%	63%	35%
Myocardial infarction	17%	17%	14%
Diabetes	23%	39%	25%
$CHADS_2$	2.1	3.5	2.1
Previous warfarin use	50%	62%	57%
INR values in therapeutic range in warfarin group	64%	55%	62.2%

ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation; $CHADS_2$, a prediction score based on whether a person is 75 years or older, has heart failure, hypertension, diabetes mellitus, and/or a prior stroke or transient ischemic attack; the higher the score, the greater the risk; HF, heart failure; HTN, hypertension; INR, international normalized ratio; RE-LY, Randomized Evaluation of Long term anticoagulant therapy; ROCKET, Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

through glomerular filtration. The half-life of dabigatran is significantly prolonged and the exposure to the drug is increased in patients with renal impairment (1.5-, 3.2-, and 6.3-fold increase in subjects with mild, moderate, and severe renal impairment) [Stangier *et al.* 2010]. This increases the risk of bleeding as there is a clear association of higher dabigatran plasma concentrations and the occurrence of bleeding events [Connolly *et al.* 2009].

Dabigatran has minimal potential drug–drug interactions since cytochrome P450 isoenzymes are not involved in its metabolism, and it neither induces nor inhibits cytochrome P450 isoenzyme activity [Stangier *et al.* 2007, 2008; Blech *et al.* 2008; Stangier, 2008]. Dabigatran etexilate, the prodrug, is a substrate of the efflux transporter P-glycoprotein (P-gp). Potent P-gp inhibitors, ketoconazole, verapamil, and amiodarone, increase prodrug absorption and lead to modest increases in dabigatran plasma concentrations [Walenga and Adiguzel, 2010].

The clinical efficacy of dabigatran was studied in the RE-LY (Randomized Evaluation of Long term anticoagulant therapy) trial [Connolly *et al.* 2009]. This study was a randomized, noninferiority trial of two blinded doses of dabigatran compared with open-label warfarin in subjects with nonvalvular atrial fibrillation and at least one risk factor for stroke (previous stroke or TIA or systemic embolism, left ventricular ejection fraction <40% or symptomatic heart failure, hypertension, age >75 years, or age 65–74 years with either diabetes mellitus or coronary artery disease). The study included 18,113 patients who were randomly assigned to receive dabigatran at one of two doses (110 or 150 mg) twice daily, or warfarin, adjusted to an INR of 2.0–3.0. Study patient characteristics are included in Table 2. The primary efficacy outcome of stroke (including hemorrhagic stroke) or systemic embolism occurred in 1.7% patients in the warfarin group, 1.5%/year in the low-dose dabigatran group, and 1.1% in the dabigatran 150 mg group. Dabigatran 110 mg met the criteria for noninferiority compared with warfarin (relative risk [RR] 0.91, 95% confidence interval [CI] 0.74–1.11), while dabigatran 150 mg was significantly more effective than warfarin (RR 0.66, 95% CI 0.53–0.82) or dabigatran 110 mg (RR 0.73, 95% CI 0.58–0.91). The superiority of dabigatran 150 mg was principally driven by reductions in strokes (RR 0.64, 95% CI 0.51–0.81). The rates of hemorrhagic stroke were significantly lower in the dabigatran 110 and 150 mg groups (0.1%/year for both doses) compared with warfarin (0.4%/year; $p < 0.001$ for both doses). Subgroup analyses of the RE-LY trial were consistent with the overall results, confirming its findings in patients with a prior stroke, in

patients with different $CHADS_2$ scores, as well as in patients undergoing cardioversion [Diener *et al.* 2010; Oldgren *et al.* 2010; Nagarakanti *et al.* 2011].

The benefit of warfarin relates directly to the time patients spend at therapeutic INR range of between 2.0 and 3.0 [Connolly *et al.* 2008]. In RE-LY, the mean percentage of the time the warfarin group had a therapeutic INR was 64%, which reflects the real-life problem with this medication. The benefits of dabigatran are greater when INR is poorly controlled [Wallentin *et al.* 2010].

The risk of major bleeding was significantly less with dabigatran 110 mg than warfarin (RR 0.80, 95% CI 0.69–0.93), and dabigatran 150 mg was not significantly different compared with warfarin (0.93, 95% CI 0.81–1.07). High-dose dabigatran was associated with significantly more major gastrointestinal bleeding than was warfarin (RR 1.50, 95% CI 1.19–1.89). Intracranial bleeding occurred less frequently with dabigatran compared with warfarin ($p < 0.001$ for both doses). The major adverse effect of dabigatran was dyspepsia, which occurred in 5.8% of the warfarin group and significantly more frequently in the dabigatran groups (11.8% for 110 mg; 11.3% for 150 mg; $p < 0.001$ for both doses) and may have contributed to the high dropout rate in patients taking dabigatran (21%) as compared with warfarin (17%) [Gage, 2009].

The rates of myocardial infarction showed a trend to be higher with dabigatran than with warfarin. They were 0.53%/year with warfarin, 0.72%/year with low-dose dabigatran ($p = 0.07$), and 0.74%/year with high-dose dabigatran ($p = 0.048$). The reason for the increase in myocardial infarction is yet to be resolved. One theory is that rather than promoting myocardial infarction, dabigatran provides less protection from myocardial infarction than warfarin. However, there is no statistical evidence for that. Dabigatran has been shown to increase urinary 11-dehydrothromboxane B_2 in patients who do not receive aspirin, suggesting a potential platelet-activating effect of dabigatran in the absence of concomitant aspirin treatment [Ezekowitz *et al.* 2007]. The clinical relevance of the small increase in myocardial infarction remains in question since cardiovascular mortality was reduced in the dabigatran group. In addition, after a reanalysis of study data the increase in myocardial infarction went from significant to nonsignificant: RR 1.27 (95% CI 0.94–1.71; $p = 0.12$) [Connolly *et al.* 2010].

Dabigatran was shown, in a small study, to be safe for use as postprocedural anticoagulation to prevent thromboembolic events following AF ablation [Winkle *et al.* 2011]. One hundred and twenty-three consecutive patients were given enoxaparin 0.5 mg/kg immediately following the procedure and was repeated 12 hours later. Patients were started on dabigatran 22 hours postablation evaluated for thromboembolic events, bleeding complications, and side effects over a 30-day follow-up period. There were no postablation strokes, TIAs, or systemic thromboembolic events in any patient. Two patients discontinued dabigatran because of gastrointestinal side effects and one because of a diffuse rash.

Dabigatran, at a dose of 150 mg twice daily, was approved for the prevention of embolic events in patients with AF with a creatinine clearance (CrCl) >30 ml/min by the US FDA. The 110 mg twice-daily dose used in the RE-LY trial did not receive FDA approval. In patients with a CrCl of 15–30 ml/min, the approved dose is 75 mg twice daily. This dose is currently marketed in Europe but was not evaluated in the RE-LY trial. There are no dosing recommendations for patients with CrCl <15 ml/min or patients on dialysis.

Factor Xa inhibitors

Rivaroxaban

Rivaroxaban is an orally administered, direct FXa inhibitor that differs from parenteral FXa inhibitors, such as fondaparinux, because it does not require antithrombin III to elicit its anticoagulant effects. FXa plays a central role in coagulation by mediating thrombin formation. One molecule of FXa is able to generate more than 1000 molecules of thrombin. Thrombin has several functions in blood coagulation, including the conversion of fibrinogen to fibrin, the activation of platelets, and the feedback activation of other coagulation factors, resulting in the amplification of its own formation. Rivaroxaban produces antithrombotic effects by decreasing the generation of thrombin, through FXa inhibition, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin itself.

Rivaroxaban has a high oral bioavailability and rapidly achieves peak plasma concentrations and anticoagulant effects (Table 1). Rivaroxaban demonstrates predictable and reproducible pharmacokinetics negating the need for routine therapeutic monitoring [Kubitza *et al.* 2005].

Rivaroxaban does prolong the prothrombin time (PT) and aPTT in a dose-dependent way with little observed interindividual variability based on age, gender, or body weight [Kubitza *et al.* 2005, 2007, 2008]. These coagulation tests can be used to monitor rivaroxaban if anticoagulant effect is in question. PT appears to be best for following the effect of rivaroxaban in clinical settings. The INR should not be used for rivaroxaban because it is only calibrated and validated for coumarins.

Rivaroxaban has a limited potential to be subject to drug–drug interactions compared with warfarin because of its dual mode of elimination. Rivaroxaban is primarily eliminated by renal excretion and approximately one-third of the drug is metabolized by the liver (CYP3A4/3A5 > CYP2J2 > non-CYP mediated hydrolysis) [Weinz *et al.* 2009]. Subjects with renal or hepatic impairment experience a decrease in the clearance of the drug, which increases rivaroxaban exposure and the risk for bleeding [Halabi *et al.* 2007; Kubitza *et al.* 2010]. Concomitant administration with drugs that are strong inhibitors or inducers of both hepatic metabolism are likely to result in a clinically relevant increase in systemic drug exposure to rivaroxaban. For instance, rivaroxaban exposure and response are significantly increased when administered concomitantly with ketoconazole and ritonavir (2.6- and 2.5-fold increase, respectively) [Eriksson *et al.* 2009]. Individuals with mild (CrCl 50–79 ml/min), moderate (CrCl 30-49 ml/min), and severe (CrCl < 30 ml/min) renal impairment, have a significant increase in the inhibition of FXa (1.5-, 1.9-, 2.0-fold, respectively) and PT prolongation (1.3-, 2.2-, 2.4-fold, respectively) compared with individuals with normal renal function [Kubitza *et al.* 2010].

The efficacy of rivaroxaban was studied in the ROCKET-AF (Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), a randomized, double-blind, double-dummy study of 14,264 patients with nonvalvular atrial fibrillation [Patel *et al.* 2011]. Patients were randomly assigned to receive either rivaroxaban 20 mg daily or warfarin adjusted to an INR of 2–3. The characteristics of study patients are included in Table 2. This noninferiority trial demonstrated that rivaroxaban was at least as effective as warfarin. In the strict intention-to-treat analysis, the primary outcome of stroke or non-CNS systemic embolism occurred in 1.7% in the rivaroxaban group and 2.2% in the warfarin group (p for noninferiority < 0.001). However, rivaroxaban was not statistically superior to warfarin in the intention-to-treat analysis (p = 0.117). In the prespecified analysis of the patients who remained on treatment over the course of the trial, rivaroxaban was superior to warfarin (1.70 *versus* 2.15; hazard ratio [HR] 0.79; 95% CI 0.65–0.95, p = 0.015). There was no significant difference in ischemic stroke, however hemorrhagic stroke was significantly reduced in the rivaroxaban group (HR 0.59, 95% CI 0.37–0.93, p = 0.024).

There were fewer intracranial bleeds with rivaroxaban (0.5 *versus* 0.7; HR 0.67; 95% CI 0.47–0.94; p = 0.019) and fewer deaths from bleeding (0.24 *versus* 0.48; HR 0.50; 95% CI 0.31–0.79; p = 0.003). However, the rivaroxaban group had more bleeds requiring transfusions (1.65 *versus* 1.32; p = 0.044) and drops in hemoglobin (2.77 *versus* 2.26; p = 0.019). Any serious adverse event occurred in approximately 40% of patients in both treatment groups and either study drug was prematurely discontinued in about 15% of patients.

In September 2011, the US FDA Cardiovascular and Renal Drugs Advisory Committee recommended the approval of rivaroxaban for the prevention of stroke in patients with atrial fibrillation.

Apixaban

Apixaban is an oral, selective, direct acting/reversible FXa inhibitor. Like rivaroxaban, it does not require antithrombin for antithrombotic activity and inhibits free as well as prothrombinase- and clot-bound FXa activity. Apixaban is rapidly absorbed with good bioavailability (Table 1). It reaches peak concentrations approximately 1–3 hours after administration reaching steady-state concentrations after 3 days. This translates into a rapid onset of action as apixaban evokes increases in aPTT and PT that parallel its plasma concentrations. Approximately 25% of the apixaban is excreted unchanged in the urine and about 25% is excreted unchanged in the feces. The remaining

drug is oxidized to several inactive metabolites compounds, partly by CYP3A4/3A5 enzymes in the liver. The multiple elimination pathways suggest that apixaban can be used in patients with hepatic or renal impairment and that the likelihood of significant drug–drug interactions is low [Wang *et al.* 2010].

The AVERROES (Apixaban *Versus* Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study was designed to compare the efficacy and safety of apixaban *versus* aspirin in patients with atrial fibrillation and who, for a variety of reasons, were not candidates for warfarin [Connolly *et al.* 2011]. This double-blind, double-dummy superiority trial enrolled 5599 patients who were randomized to receive either apixaban 5 mg twice daily or aspirin, at a dose of 81–324 mg daily. The study population in the AVERROES trial was similar to the patient population in the RE-LY trial. The study was stopped early after a predefined interim analysis showed clear evidence of a reduction in stroke and systemic embolism. Apixaban treatment was associated with a 55% reduction in stroke (ischemic or hemorrhagic) or systemic embolism compared with aspirin over a mean follow up of 1.1 years (1.6% *versus* 3.7%; HR 0.45; 95% CI 0.32–0.62; $p < 0.001$). The benefit of apixaban was most apparent in patients with $CHADS_2$ scores of 3 or greater.

The benefit of apixaban also occurred without an increase in the risk of major bleeding compared with aspirin (1.4% *versus* 1.2%; HR 1.13; 95% CI 0.74–1.75; $p = 0.57$). This includes no increased risk of fatal bleeds (0.1% *versus* 0.2%; $p = 0.53$) or intracranial hemorrhage (0.4% *versus* 0.4%; $p = 0.69$). Serious adverse events of any kind occurred more frequently in the aspirin group and events leading to permanent discontinuation of the study medication were significantly lower in the apixaban group (17.9%/year *versus* 20.5%/year; $p = 0.03$).

Apixaban was compared head-to-head with warfarin at reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism in AF patients in the ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation) trial [Granger *et al.* 2011]. The trial randomized 18,201 AF patients to apixaban (5 mg orally twice daily) or warfarin (target INR of 2.0–3.0). The study population in the ARISTOTLE trial was similar to the study populations in the AVERROES and RE-LY trials. After a median follow up of 1.8 years, apixaban was associated with a 21% reduction in the risk of stroke or systemic embolism (1.27% *versus* 1.6%; 95% CI 0.66–0.95; $p = 0.01$), a 31% reduction in major bleeding (2.1% *versus* 3.1%; 95% CI 0.60–0.80; $p < 0.001$), and an 11% reduction in all-cause mortality (3.52% *versus* 3.94%; 95% CI 0.80–0.99; $p = 0.047$). As with dabigatran and rivaroxaban, apixaban resulted in lower rates of hemorrhagic stroke (HR 0.51; 95% CI 0.35–0.75; $p < 0.001$) and intracranial hemorrhage (HR 0.42; 95% CI 0.30–0.58; $p < 0.001$). Conversely to dabigatran and rivaroxaban, there was no increase in gastrointestinal bleeding with apixaban compared with warfarin.

Edoxaban

Edoxaban is a direct FXa inhibitor with a rapid onset of action, short half-life, 8–10 hours, and multiple elimination pathways [Ogata *et al.* 2010]. The majority of drug is eliminated via renal excretion and exposure to edoxaban increases in patients with renal dysfunction [Ogata *et al.* 2010]. Edoxaban was studied in a phase II trial that randomized 1146 subjects with AF (follow up of 3 months) to one of four doses of edoxaban or open-label warfarin titrated to INR 2.0–3.0 [Weitz *et al.* 2010]. Based on this trial, the 30 mg once-daily and 60 mg once-daily doses of edoxaban were selected for comparison with warfarin in a phase III double-blind, double-dummy study of patients with atrial fibrillation. The ENGAGE AF-TIMI (Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation) is a noninferiority trial recruiting approximately 16,500 patients with AF and moderate to high risk (CHADS ≥ 2) of stroke [Ruff *et al.* 2010]. The estimated completion date is 2012.

Betrixaban

Betrixaban is an oral direct FXa inhibitor with a long half-life (19 h) that allows for once-daily dosing [Zhang et al. 2009]. Betrixaban is primarily eliminated unchanged in the bile with minimal renal excretion (<5%), which may make it particularly suitable for patients with renal failure. It is also minimally metabolized through the CYP P450 enzyme system, which may result in a low potential for drug–drug interactions [Zhang *et al.* 2009]. The safety and tolerability of betrixaban for stroke prevention was evaluated in 508

patients with AF in a phase II dose-ranging study [Ezekowitz, 2010]. Patients with nonvalvular atrial fibrillation (n = 127) were randomized to one of three doses of betrixaban (40 mg, 60 mg, 80 mg) *versus* warfarin, with a goal INR of 2–3. The three tested doses of betrixaban appeared to be well tolerated. Bleeding was lowest in the betrixaban 40 mg group, compared with higher-dose betrixaban or warfarin.

New anticoagulants versus warfarin

Warfarin has several decades of proven efficacy in AF-related stroke prevention but the drug's numerous drawbacks make its implementation difficult for practitioners and patients (Table 3). Owing to this, warfarin is underused, suboptimally applied, and often discontinued in patients at high risk of stroke. An anticoagulant with equal efficacy, but with a better safety profile and/or ease of use is a big step in the management of AF patients. Rivaroxaban was shown to have an efficacy similar to warfarin, dabigatran (150 mg dose) was statistically superior to warfarin in the prevention of stroke or systemic embolic events and apixaban reduced stroke or systemic embolism and overall mortality compared with warfarin. These drugs may have a better safety profile than warfarin. All three new anticoagulants have shown a large reduction in intracranial hemorrhage compared with warfarin. This may be related to warfarin's inhibition of multiple coagulation factors or an interaction with tissue factor VIIa complexes in the brain [Mackman, 2009; Granger *et al.* 2011]. Apixaban had a substantially lower risk of bleeding and with lower rates of discontinuation. Dabigatran, on the other hand, was more likely to cause gastrointestinal bleeding and nonhemorrhagic side effects (e.g. dyspepsia) leading to drug discontinuation. None of the new anticoagulants have data in AF-patients with significant valvular disease requiring valve replacement. Warfarin remains the drug of choice in this population until data become available on the new agents.

The safety and efficacy of warfarin are dependent on the time patients spend in the therapeutic INR range [Veeger *et al.* 2006]. The incidence of adverse events increases substantially as the INR goes above or below therapeutic range [White *et al.* 2007]. Maintaining a therapeutic INR can be difficult, however new mechanisms are emerging that may improve the safety and efficacy of warfarin and reduce the inconvenience of warfarin management [Harper and Pollock, 2008; Ryan *et al.* 2008, 2009]. This is not an issue with the new anticoagulants since they do not have warfarin's narrow therapeutic window. They are given as a fixed dose and do not require persistent monitoring making them much more convenient. A major advantage of new anticoagulants is that they are less susceptible to the dietary and drug interactions that confound warfarin management. However, even though the need for INR monitoring is considered a detriment of warfarin therapy, it does provide an objective way to assess and respond to nonadherence and a monitoring tool in case of bleeding or thrombosis. The inability to accurately monitor the new anticoagulants may be troublesome in patients with chronic kidney disease whose dosing needs will vary according to renal function. However, PT may be used to measure the effect of rivaroxaban and anti-FXa may be used to measure apixaban in clinical settings.

A major disadvantage of the new anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. Patients who require a rapid reversal of warfarin can be administered vitamin K. Prothrombin complex concentrate (PCC) has been shown to reverse the anticoagulant effect of rivaroxaban in healthy subjects [Eerenberg *et al.* 2011]. The effects of dabigatran were not reversed with PCC and apixaban has yet to be studied. A large clinical study on anticoagulated patients with bleeding events is necessary before implementing PCC into clinical practice. Dabigatran blood levels drop fairly rapidly after stopping the medication, so an antidote may not be essential. In the event of an acute overdose (<1–2 hours), the administration of activated charcoal may be helpful in adsorbing dabigatran [Van Ryn *et al.* 2010]. If bleeding is catastrophic it is possible to dialyze the patient, because dabigatran is dialyzable.

To the advantage of the new anticoagulants, the rapid onset/offset of these drugs allows them to be stopped before a procedure and restarted without bridging, whereas warfarin requires 3–5 days interruption before a procedure, often with bridging therapy to deal with the additional 3–5 days to get back to therapeutic levels. Price will also be a major factor in deciding the role for the new anticoagulants. Dabigatran and rivaroxaban will cost over US$200 per month while no price yet exists for apixaban. Despite the high cost, two

Table 3. Advantages and disadvantages of anticoagulants.

	Pros	Cons
Warfarin	Long history of use Once-a-day dosing Long half-life Antidote for reversal Affordable	Narrow therapeutic window Requires frequent monitoring Considerable amount of time is required for its control Numerous drug and food interactions Genetic variation Slow onset of action Requires bridging during surgery Intracranial hemorrhage risk Procoagulant effect through protein C and protein S depletion
Dabigatran	Fixed dosing Rapid onset of action Predictable PK/PD Lower ICH risk compared with warfarin Dialyzable Minimal food and drug interactions No monitoring requirement Can be stopped and restarted for surgery without bridging	Twice-a-day dosing Gastrointestinal hemorrhage Dyspepsia No reliable monitoring in case of bleeding or thrombosis Difficult to validate patient compliance No known antidote for reversal The need for dose adjustment for renal impairment Lack of long-term safety data Cost
Rivaroxaban	Fixed, once-a-day dosing Predictable PK/PD Effects reversed with prothrombin complex concentrate No monitoring requirement Lower ICH risk compared with warfarin Minimal food and drug interactions PT can be used to measure drug's effect	Lack of long-term safety data Dosing restrictions for renal impairment No established therapeutic range Difficult to validate patient compliance Cost (projected)
Apixaban	Superior to warfarin in preventing strokes Lower overall bleeding risk compared to warfarin Fixed dosing Rapid onset of action Predictable PK/PD No monitoring requirement Anti-FXa can be used to measure drug's effect Minimal food and drug interactions	Twice-a-day dosing No known antidote for reversal Lack of long-term safety data Difficult to validate patient compliance Cost (projected)

FXa, factor Xa; ICH, intracranial hemorrhage; PK/PD, pharmacokinetic/pharmacodynamic; PT, prothrombin time.

cost-effectiveness analyses have shown that dabigatran may be a cost-effective alternative to warfarin [Freeman *et al.* 2010; Sorensen *et al.* 2011].

Both new and old anticoagulants have their advantages and disadvantages. Little is to be gained by switching a well-controlled patient from warfarin to new anticoagulants. However, the new anticoagulants would be of benefit in patients with labile INRs and in those who do not have an anticoagulation management program to sustain routine monitoring of INR or do not wish to take warfarin.

Comparison of new anticoagulants

At this time, there is no scientifically valid way to compare apixaban, rivaroxaban, and dabigatran as the trials evaluating their efficacy had different designs and study populations. Dabigatran and rivaroxaban have undergone thorough peer and FDA review. Apixaban data have not yet undergone the scrutiny that dabigatran and rivaroxaban data have. The ideal comparison of these drugs would be in a large, randomized, head-to-head comparative study. However, with the amount of revenue that could potentially be lost by the manufacturers if their drug was found inferior, the likelihood of such a trial is very unlikely. Dabigatran has shown difficulties with dyspepsia and gastrointestinal hemorrhage, while neither rivaroxaban nor apixaban seemed to have this particular adverse-event profile in clinical trials. The safety profiles of these drugs will become clearer with more widespread use. The data are strongest for apixaban. It was superior to warfarin and aspirin in the reduction of stroke and systemic embolism but was the only one of the three to also show a significant reduction in bleeding as well. There was a strong trend towards a reduction in mortality with dabigatran and rivaroxaban, but apixaban had a significant mortality reduction compared to warfarin. Of the new agents only rivaroxaban is a once-a-day medication, which might be more convenient and able to increase adherence.

Personal preference and provider comfort will likely guide the decision to use one drug over another. However, selection may become clearer as these drugs are used more extensively.

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