

A Clinically Oriented Review of the Landmark Clinical Trials Comparing Warfarin and Aspirin to Novel Oral Anticoagulants in Atrial Fibrillation

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Abstract

Objective: Until recently, oral anticoagulant drug options for patients with atrial fibrillation were limited to vitamin K antagonists. Over the last few years, three novel oral anticoagulants have been approved by the FDA for prevention of stroke and systemic embolism in atrial fibrillation and a fourth drug is currently under consideration for FDA approval. Recent large clinical trials have compared these four novel oral anticoagulants to warfarin or aspirin and found them to be non-inferior or superior for the prevention of stroke and systemic embolism in atrial fibrillation without increasing the risk of major bleeding. Furthermore, all four novel oral anticoagulants have been shown to significantly decrease the risk of intracranial hemorrhage compared to warfarin. Understanding the similarities and differences among these new anticoagulant drugs is of paramount importance when choosing the optimal anticoagulant for an individual patient. Detailed evaluation and understanding of the subtle nuances in clinical outcomes between the various anticoagulants in different trials allows the practicing clinician to make a better informed decision when recommending oral anticoagulation to patients. This review provides a clinically relevant discussion of the landmark novel oral anticoagulant trials in atrial fibrillation and provides specific recommendations to inform the practicing clinician.

Keywords: Dabigatran; Rivaroxaban; Apixaban; Edoxaban; Atrial Fibrillation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults and it increases a patient's risk of stroke and death [1-3]. Specifically, AF increases the risk of ischemic stroke by a factor of four to five [2]. AF accounts for up to 15% of strokes in persons of all ages and 30% in persons over the age of 80 [3]. To reduce these risks, vitamin K antagonists (VKAs) such as warfarin or antiplatelet agents (i.e. aspirin, clopidogrel, etc.) are recommended for AF patients [4]. VKA therapy has been shown to be more effective than aspirin for the prevention of stroke in patients with AF [5]. VKAs are highly effective and reduce the risk of stroke by about two thirds [6]. However, VKA therapy is complicated by multiple food and drug interactions, the need for frequent laboratory monitoring and dose adjustment, a narrow

window for a therapeutic benefit and significant intra- and inter-patient dose variability [5-7]. Because of these limitations, large surveys indicate that at least one third of patients who are considered to be ideal candidates for anticoagulation therapy are not receiving it [8-10]. Therefore, VKAs are often not started in patients who would benefit from them or once started, are discontinued at a high rate [10, 11]. Even among patients who are able to continue on VKAs, many receive inadequate anticoagulation due to the aforementioned issues with warfarin [12]. Maintaining the international normalized ratio (INR) in the therapeutic range is difficult and for many patients is achieved less than 60% of the time, which ameliorates the benefits of VKA therapy [13]. Although inferior to VKAs, aspirin reduces the risk of stroke in AF patients by about 20% and is useful for patients deemed to be at lower risk for stroke or for whom VKA therapy is considered unsuitable [6]. The addition of clopidogrel to aspirin further reduces the risk of stroke by 28%, but the combination increases the risk of major hemorrhage (relative risk 1.57) [14]. Given these

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limitations, there has been considerable interest in developing oral anticoagulants that are noninferior or superior to VKAs with respect to efficacy and safety without the pharmacodynamic and pharmacokinetic limitations associated with VKAs

Recently, several large clinical trials have compared warfarin or aspirin to novel oral anticoagulants (NOAs) [15-19]. These studies have generated considerable interest in the use of NOAs for the treatment AF patients. These trials appear to demonstrate that NOAs are at least as beneficial as warfarin, at least as safe as warfarin and in some cases superior to warfarin in efficacy and/or safety. However, these trials have important subtleties that clinicians considering prescribing NOAs should understand. This review focuses on the major landmark oral anticoagulation trials in AF and specifically examines important similarities and differences between the trials to better inform physicians prescribing NOAs.

Dabigatran and the RE-LY trial

Dabigatran etexilate mesylate is a synthetic, non-peptide, oral prodrug which is hydrolyzed by esterases in plasma and other sites to form the active competitive direct thrombin inhibitor (DTI), dabigatran [20]. The Food and Drug Administration (FDA) approved dabigatran to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF and at least one risk factor for stroke [20, 21]. After oral administration, dabigatran reaches peak plasma concentration and anticoagulant activity within 0.5-2 hours (Table 1) [22]. The half-life of dabigatran is 12-17 hours in healthy volunteers with a creatinine clearance (CrCl) of >60 ml/minute [23, 24]. Dabigatran is 35% protein bound and 80% of the drug is eliminated by the kidneys [20, 22, 25]. The use of dabigatran is not recommended in patients with CrCl < 15 mL/minute or in patients on dialysis [20]. Unlike VKAs, dabigatran has a predictable pharmacokinetic and pharmacodynamics profile, which allows for a fixed-dosing regimen without the need for routine laboratory monitoring and frequent dose adjustments.

The dabigatran dose was blinded but the use of warfarin was unblinded. Concomitant use of aspirin (<100 mg per day) or other antiplatelet agents were permitted. Of note, the 110 mg BID dose was not approved for use in the United States and will not be discussed in this review [21].

To be enrolled in RE-LY, patients had AF and at least one of the following characteristics described in Table 2 (inclusion criteria closely resemble CHADS₂ criteria). The exclusion criteria (Table 2) predominantly focus on omitting subjects with co-morbidities that would increase the patient's risk of bleeding. Valvular AF, an exclusion criterion, was defined as a prosthetic valve or "hemodynamically relevant valve disease" [15]. More than 18,000 patients were enrolled in the RE-LY trial with a mean age of 71 and the mean CHADS₂ score was 2.1 [15].

Clinical outcomes

The primary outcome of stroke or systemic embolism occurred at a rate of 1.11% per year in patients receiving 150 mg of dabigatran compared with a rate of 1.69% per year in patients receiving warfarin [15]. Therefore, the 150 mg dose of dabigatran was determined to be superior to warfarin for preventing the primary endpoint by reducing the annual relative risk of stroke by 34% (RR 0.66; P<0.001). Dabigatran reduced the annual relative risk of hemorrhagic stroke by 74% as the rates of hemorrhagic stroke were 0.38% per year in the warfarin group, compared with 0.10% per year in the group that received 150 mg of dabigatran (RR 0.26; P<0.001). The rate of myocardial infarction (MI) was higher in the dabigatran group at 0.74% per year (RR 1.38, P=0.048) compared with 0.53% per year with warfarin. The rates of death from any cause were 4.13% per year with warfarin, as compared with 3.64% per year with dabigatran (RR 0.88; P=0.051). Although this outcome just missed statistical significance, this strongly suggests that dabigatran may offer a mortality benefit over warfarin.

Drug (Target)	Standard Dosage	Reduced Dose	Oral Bioavailability	Half-life (hours)	% renal excretion	Time to peak plasma concentration (hours)
Dabigatran (Thrombin)	150 mg BID	75 mg BID (110 mg BID not approved in U.S.)	6.5%	14-17	80%	0.5-2
Rivaroxaban (Factor Xa)	20 mg daily	15 mg daily	80%	9-13	66%	2-4
Apixaban (Factor Xa)	5 mg BID	2.5 mg BID	66%	8-15	25%	3
Edoxaban (Factor Xa)	60 mg or 30 mg daily	30 mg or 15 mg daily	50%	9-11	35%	1-2

Table 1. Pharmacologic properties of novel oral anticoagulants

Abbreviations: BID, Twice daily

The RE-LY trial was a randomized study designed to compare two fixed doses of dabigatran versus open-label use of warfarin in patients who had AF and were at increased risk for stroke [26]. Patients were randomly assigned 110 mg dabigatran twice daily (BID), 150 mg dabigatran BID or warfarin.

Bleeding and adverse events

There was no statistical difference in the rate of major bleeding between warfarin and dabigatran [15]. The warfarin group had a 3.36% per year rate of major bleeding as compared

with 3.11% per year in the dabigatran group ($P=0.31$). However, sub-analyses revealed differences between the types of bleeding. The warfarin group had a statistically higher annual rate of life-threatening bleeding, intracranial bleeding, and major or minor bleeding (1.80%, 0.74%, and 18.15%, respectively) than did patients in the dabigatran (1.45%, 0.30%, and 16.42%, respectively; all $P<0.05$). Conversely, there was a significantly higher rate of major gastrointestinal bleeding with dabigatran than with warfarin (1.51% vs. 1.02%, $P=0.007$). The RE-LY authors created the “net clinical benefit outcome” which consisted of major vascular events, major bleeding and death. The rates of this combined outcome were 7.64% per year with warfarin and 6.91% per year with dabigatran ($P=0.04$). The only adverse medication side effect that was significantly more common with dabigatran than with warfarin was dyspepsia. Dyspepsia occurred in 11.3% of the 150 mg dabigatran group and 5.8% of the warfarin group ($P<0.001$). In our clinical experience, dyspepsia is a common cause for discontinuing dabigatran.

lower rates of stroke and systemic embolism and had a similar rate of major hemorrhage compared to warfarin. This represents the first study showing a drug to be better than warfarin without an increased risk of bleeding. Previous trials showed that the combination of clopidogrel and aspirin was more effective than aspirin alone [14] but less effective than warfarin [27]. Another trial demonstrated that subcutaneous idraparinux was more effective than warfarin but was associated with a substantially higher risk of bleeding [28]. The rate of myocardial infarction was higher with dabigatran than with warfarin. It has previously been shown that warfarin reduces the risk of myocardial infarction [29]. It is unclear why dabigatran patients had a greater rate of myocardial infarction, but one hypothesis suggests that warfarin, may provide better protection against coronary ischemic events than inhibition of thrombin alone. The worst complication of warfarin therapy is intracranial hemorrhage and warfarin doubles the risk of intracranial hemorrhage as compared with aspirin [30]. Since dabigatran is associated with less intracranial hemorrhage

Trial name	Novel oral anticoagulant	Inclusion criteria (AF and...)	Common exclusion criteria	Unique exclusion criteria	Definition of Valvular Atrial Fibrillation	Mean CHADS ₂ score
RE-LY	Dabigatran	<ul style="list-style-type: none"> •Prior TIA/CVA •LV EF $\leq 40\%$ or NYHA \geq II last 6 months •Age ≥ 75 •Age 65-74 plus DM, HTN or CAD 	<ul style="list-style-type: none"> •AF secondary to a reversible disorder •Valvular AF •Recent stroke (within 7-14 days) 	<ul style="list-style-type: none"> •Severe stroke within 6 months •CrCl < 30 ml/min 	<ul style="list-style-type: none"> •Prosthetic valve •Hemodynamically relevant valve disease 	2.1
ROCKET-AF	Rivaroxaban	<ul style="list-style-type: none"> •Prior TIA/CVA or •At least two of the following risk factors: <ul style="list-style-type: none"> –Clinical heart failure or LV EF $\leq 35\%$ –Hypertension –Age ≥ 75 –Diabetes 	<ul style="list-style-type: none"> •Predisposition to bleeding •ESRD •Active liver disease •Pregnancy •Anemia (Hemoglobin < 10 g/dL) 	<ul style="list-style-type: none"> •Platelet count $< 90,000/\mu\text{L}$ •Severe stroke within 3 months •CrCl < 30 ml/min •ASA > 100 mg daily, •ASA and thienopyridine 	Hemodynamically significant mitral stenosis or prosthetic valve	3.5*
ARISTOTLE	Apixaban	<ul style="list-style-type: none"> •Prior TIA/CVA •Age ≥ 75 •Symptomatic CHF or LV EF $\leq 40\%$ •Diabetes •Hypertension 	<ul style="list-style-type: none"> •Thrombocytopenia ($< 100,000/\mu\text{L}$) •Indication for AC other than AF •Active endocarditis 	<ul style="list-style-type: none"> •ASA > 165 mg •ASA and thienopyridine •SCr > 2.5 mg/dL •CrCl < 25 ml/min •Hgb < 9 g/dL 	<ul style="list-style-type: none"> •Moderate or severe mitral stenosis •Prosthetic valve 	2.1
AVERROES	Apixaban	<ul style="list-style-type: none"> •Age ≥ 50, CHADS₂ ≥ 1 or PAD and demonstrated or expected to be unsuitable for warfarin 	<ul style="list-style-type: none"> •Chronic, uncontrolled hypertension •Limited life expectancy •Acute coronary syndrome 	<ul style="list-style-type: none"> •Thienopyridine •Open-label ASA discouraged but allowed < 100 mg •SCr > 2.5 mg/dL •CrCl < 25 ml/min 	<ul style="list-style-type: none"> •Valvular disease requiring surgery 	2.0
ENGAGE AF-TIMI 48	Edoxaban	<ul style="list-style-type: none"> •CHADS₂ ≥ 2 	<ul style="list-style-type: none"> •Coronary revascularization •Inability to adhere to study protocol 	<ul style="list-style-type: none"> •CrCl < 30 ml/min •ASA and thienopyridine •Stroke within 30 days 	<ul style="list-style-type: none"> •Moderate or severe mitral stenosis •Prosthetic valve 	2.8

Table 2. Summary of the important characteristics of the landmark trials of novel oral anticoagulants in atrial fibrillation

*Subjects with score of 2 limited to 10% of total study population

Abbreviations: AF, atrial fibrillation; TIA, transient ischemic attack; CVA, cerebrovascular accident; LV EF, left ventricular ejection fraction, NYHA, New York Heart Association; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; ESRD, end stage renal disease; AC, anticoagulation; CrCl, creatinine clearance; ASA, aspirin; SCr, serum creatinine; Hgb, hemoglobin.

Discussion

The 150 mg dose of dabigatran was associated with

than warfarin, this may represent an important advantage favoring dabigatran. There was an increase in the rate of gastrointestinal bleeding with dabigatran, despite overall lower rates

of bleeding at other sites. It is unclear why dabigatran increases gastrointestinal bleeding but decreases intracranial bleeding.

Rivaroxaban and the ROCKET AF trial

Rivaroxaban is an oral, direct factor Xa (FXa) inhibitor. It reaches maximum plasma concentrations, 2–4 h after ingestion [31]. The bioavailability of rivaroxaban is dose-dependent where the estimated bioavailability of the 10 mg dose is 80–100 % compared to 66 % for the 20 mg dose [32]. The bioavailability of the 20 mg dose can be moderately increased, and inter-patient variability decreased, by administering with food [32]. Rivaroxaban has a high affinity (92–95 % in vitro) plasma protein binding indicating that rivaroxaban is not expected to be dialyzable like dabigatran [31, 33]. The half-life of rivaroxaban is 5–9 h in healthy young patients and 11–13 h in elderly patients [31]. The elimination of rivaroxaban occurs by both renal excretion (36%) and hepatic metabolism [31].

The ROCKET AF trial was designed as a noninferiority trial to compare rivaroxaban against warfarin for the prevention of stroke and systemic embolism in nonvalvular AF patients who were at moderate-to-high risk for stroke [16, 34]. Patients were randomized to rivaroxaban 20 mg daily (15 mg daily in patients with a creatinine clearance of 30–49 ml/min) or warfarin. Elevated stroke risk was defined as a CHADS₂ score of ≥ 2 (specific criteria outlined in Table 2). Since this trial was intended to study patients at moderate-to-high risk of stroke, the number of patients with a CHADS₂ score of 2 based on risk factors (no prior history of stroke/TIA) was limited to 10%. The majority of patients were required to have had either a previous thromboembolic event or ≥ 3 risk factors. The mean CHADS₂ score was 3.5. The definition of valvular AF was defined as hemodynamically significant mitral valve stenosis or prosthetic heart valve. This is less restrictive than the RE-LY trial which defined valvular AF as hemodynamically relevant valve disease. The exclusion criteria outlined in Table 2 included “indication for anticoagulant therapy for a condition other than atrial fibrillation.” Subsequently, rivaroxaban has received FDA approval for use in other thrombotic diseases, including the treatment and prevention of deep vein thrombosis and pulmonary embolism [35–37].

Clinical outcomes

The primary endpoint (stroke or systemic embolism) occurred at a rate of 2.1% per year in the rivaroxaban group and 2.4% per year in the warfarin group indicating that rivaroxaban was noninferior but not superior to warfarin ($P < 0.001$ for noninferiority; $P = 0.12$ for superiority). There was also no difference between the two groups with respect to myocardial infarction or overall mortality [16].

Bleeding and adverse events

Rates of major bleeding, as defined by the International Society on Thrombosis and Haemostasis criteria (ISTH), were not significantly different between the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively; $P = 0.58$). However, individual analyses of the various ISTH criteria revealed differences between rivaroxaban and warfarin. Decreases in hemoglobin levels of ≥ 2 g/dl and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent with rivaroxaban (Table 3). The rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group indicating an annual relative risk

reduction of 33% (0.5% vs. 0.7% per year; HR 0.67; $P = 0.02$). Major gastrointestinal bleeding was more common in the rivaroxaban group compared to the warfarin group (3.2% vs. 2.2%, $P < 0.001$).

Discussion

Using the prespecified statistical-analysis plan, rivaroxaban was no inferior to warfarin with respect to the prevention of stroke or systemic embolism in patients who were at moderate to high risk for stroke and there was no difference in the rates of clinically relevant bleeding. However, using an intention-to-treat analysis, there were significantly fewer primary events (stroke or systemic embolism) in patients taking rivaroxaban compared to patients taking warfarin during the treatment period (1.7% versus 2.2%, $P = 0.02$ for superiority). In other words, if the patient was able to remain compliant with the study drug, rivaroxaban was superior to warfarin. Although the rates of clinically relevant bleeding were similar between rivaroxaban and warfarin, fatal bleeding and bleeding in critical anatomical sites occurred less frequently with rivaroxaban, predominantly due to lower rates of intracranial bleeding. Bleeding in critical anatomical sites was defined as intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome. However, gastrointestinal bleeding occurred more frequently with rivaroxaban as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion.

Apixaban and the AVERROES trial

Apixaban is a direct oral FXa inhibitor with rapid absorption (0.5–2 hours to reach maximum plasma concentration), a 12-hour half-life, and 25% renal excretion (Table 1). Apixaban is metabolized by the CYP3A4 in the cytochrome P450 system and is 87% protein bound making it difficult to dialyze [38, 39].

The AVERROES trial was designed to determine the efficacy and safety of apixaban, as compared with aspirin for the treatment of AF patients who were considered to be unsuitable for warfarin therapy [17, 40]. The primary efficacy outcome was the occurrence of stroke or systemic embolism. Patients were randomly assigned to receive apixaban at a dose of 5 mg BID or aspirin at a dose ranging from 81 to 324 mg per day. A reduced dose of apixaban (2.5 mg BID) was used for patients who met two of the following criteria: age ≥ 80 , body weight ≤ 60 kg or a serum creatinine level of ≥ 1.5 mg/dl. The dose of aspirin was selected at the discretion of the local investigator. Patients were eligible for enrollment in AVERROES if they were age ≥ 50 , had documented AF and at least one risk factor for stroke (see Table 2). In addition, patients could not be receiving VKA therapy, either because it had already been demonstrated to be unsuitable for them or because it was expected to be unsuitable [17].

Clinical outcomes

The AVERROES trial was terminated early because of safety concerns as the investigators observed a treatment benefit in favor of apixaban for the primary outcome that exceeded 4 standard deviations (P value = 0.000002). The primary outcome (stroke or systemic embolism) occurred at a rate of 1.6% per year among patients taking apixaban and 3.7% per year among patients on aspirin (HR 0.45; $P < 0.001$). The rate of death was lower in the apixaban group (3.5% per year) than in the aspirin group (4.4% per year), although this did not quite meet statistical significance (HR 0.79; $P = 0.07$).

The rate of hospitalization for cardiovascular causes was significantly lower in the apixaban group (12.6% per year) than in the aspirin group (15.9% per year; HR 0.79; $P < 0.001$).

tion of stroke, with a risk of bleeding that was similar to that of aspirin, indicating that its ratio of benefit to risk may be better than that of VKAs and that it could be useful in these moder-

Trial	Study Drugs	Primary endpoint	Secondary Outcomes	Bleeding	Mortality
RE-LY	Dabigatran vs. warfarin	<ul style="list-style-type: none"> The 150 mg dose was superior to warfarin for the prevention of stroke 	<ul style="list-style-type: none"> Less hemorrhagic, fatal, ischemic, or disabling stroke Increased risk MI 	<ul style="list-style-type: none"> Similar major bleeding rates Less ICH, minor bleeding, life-threatening bleeding More GIB 	<ul style="list-style-type: none"> Strong trend towards all-cause mortality benefit ($P = 0.051$) Less vascular death ($P = 0.04$)
ROCKET-AF	Rivaroxaban vs. warfarin	<ul style="list-style-type: none"> Rivaroxaban is noninferior to warfarin for the prevention of stroke 	<ul style="list-style-type: none"> Similar rates of ischemic stroke Less hemorrhagic stroke Similar rate of MI Less stroke + MI + vascular death 	<ul style="list-style-type: none"> Similar major and nonmajor bleeding rates Less ICH, critical and fatal bleeding Increased rate of requiring transfusion, more GIB 	<ul style="list-style-type: none"> Trend towards mortality benefit ($P = 0.07$)
ARISTOTLE	Apixaban vs. warfarin	<ul style="list-style-type: none"> Apixaban was superior to warfarin for the prevention of stroke 	<ul style="list-style-type: none"> Similar rates of ischemic stroke Less hemorrhagic stroke Similar rate of MI 	<ul style="list-style-type: none"> Less ICH, major and minor bleeding Similar rate of GIB 	<ul style="list-style-type: none"> Less death from any cause ($P = 0.047$)
AVERROES	Apixaban vs. aspirin	<ul style="list-style-type: none"> Early study termination due to clear benefit in favor of apixaban 	<ul style="list-style-type: none"> Less ischemic, disabling or fatal stroke risk Less hospitalization for CV cause Similar hemorrhagic stroke risk 	<ul style="list-style-type: none"> Similar rates of ICH, GIB, major, fatal and nonmajor bleeding Increased risk of minor bleeding 	<ul style="list-style-type: none"> Trend towards mortality benefit ($P = 0.07$, study terminated early)
ENGAGE AF-TIMI 48	Edoxaban* vs. warfarin	<ul style="list-style-type: none"> Both doses noninferior to warfarin for the prevention of stroke Less hemorrhagic stroke (both doses) More ischemic stroke with 30 mg dose 	60 mg dose: <ul style="list-style-type: none"> Lower rate of stroke + CV death or stroke + death Less MACE Similar rate of MI 	<ul style="list-style-type: none"> Lower rates of bleeding for both doses except 60 mg dose had increased GIB risk 	<ul style="list-style-type: none"> Decreased rate of CV death (both doses) Decreased rate of all-cause mortality with 30 mg dose

Table 3. Summary of the important outcomes of the landmark trials of novel oral anticoagulants in atrial fibrillation

*Not currently approved, awaiting evaluation by FDA

Abbreviations: MI, myocardial infarction; CV, cardiovascular; MACE, major adverse cardiac events; ICH, intracerebral hemorrhage; GIB, gastrointestinal bleeding

Bleeding and adverse events

There was no difference in the rate of major bleeding events (defined by ISTH criteria) among patients taking apixaban or aspirin (1.4% vs. 1.2% per year; $P = 0.57$). However, there were 188 minor bleeding events on apixaban compared to 153 minor bleeding events on aspirin (HR 1.24; $P = 0.05$). The composite rate of stroke, systemic embolism, myocardial infarction, death from vascular causes, or major bleeding was significantly reduced with apixaban, as compared with aspirin (intention-to-treat analysis, 5.3% per year vs. 7.2% per year; HR 0.74; $P = 0.003$; on-treatment analysis, 4.0% per year vs. 6.3% per year; HR 0.64; $P < 0.001$). After two years, the rates of permanent discontinuation of apixaban were 17.9% per year versus 20.5% per year in the aspirin group (HR 0.88; $P = 0.03$). Significantly fewer patients in the apixaban group had a serious adverse event (22% vs. 27%, $P < 0.001$), which was driven by a lower rate of ischemic stroke [17].

Discussion

Patients were eligible for the AVERROES trial if their physicians considered VKA therapy to be unsuitable for them. In patients for whom VKA therapy was considered unsuitable, apixaban, as compared with aspirin, reduced the risk of stroke or systemic embolism by more than 50%, without a significant increase in the risk of major bleeding. In the current study, apixaban was much more effective than aspirin for the preven-

ate-risk patients. Apixaban as compared with aspirin reduced the risk of ischemic stroke by more than 60% but did not appear to increase the risk of hemorrhagic stroke. To evaluate the net benefit of apixaban, a composite outcome that included ischemic events and major bleeding was used. The rate of this outcome was significantly reduced with apixaban as compared with aspirin (5.3% per year vs. 7.2% per year, $P = 0.003$). In this study, the rate of death with apixaban as compared with aspirin was reduced by 1% per year ($P = 0.07$). Among patients with AF, hospitalization for cardiovascular causes is strongly associated with increased mortality and has a major impact on health care costs [41]. In our study, the rate of hospitalization for cardiovascular causes was significantly reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, $P < 0.001$). Apixaban was also associated with fewer serious adverse events and lower rates of discontinuation of medication, indicating that it had an acceptable side-effect profile as compared with aspirin. On the basis of the results of the intention-to-treat analysis, treating 1000 patients for 1 year with apixaban rather than with aspirin would prevent 21 strokes or systemic emboli, 9 deaths, and 33 hospitalizations for cardiovascular causes, at the cost of 2 major bleeding events [17]. In summary, among patients with atrial fibrillation who are at high risk for stroke and for whom VKA therapy is unsuitable, apixaban, as compared with aspirin, substantially reduced the risk of stroke, with no significant increase in the risk of major bleeding or intracranial bleeding. The net clinical

benefit of apixaban in these patients appears to be substantial.

Other antithrombotic agents have been compared with aspirin for the treatment of patients with atrial fibrillation. In ACTIVE A, the addition of clopidogrel to aspirin reduced the risk of stroke by 28%, [14] and in meta-analyses of randomized trials of vitamin K antagonist therapy as compared with aspirin, vitamin K antagonist therapy reduced the risk of stroke by 39% [30, 42]. These indirect comparisons suggest that apixaban is more effective than clopidogrel plus aspirin.

Apixaban and the ARISTOTLE trial

In the ARISTOTLE trial [43], apixaban was compared to warfarin for the prevention of stroke in AF patients with at least one additional risk factor for stroke. The primary outcome was stroke or systemic embolism and the primary safety outcome was major bleeding. ARISTOTLE was designed as a noninferiority trial where patients were randomly assigned to treatment with apixaban or warfarin [43]. The apixaban dosing in ARISTOTLE was 5 mg BID. The same criteria for using a reduced apixaban dose in the AVERROES trial were used in the ARISTOTLE trial (Table 4). The median age was 70, the mean CHADS₂ score was 2.1 and 4.7% of the apixaban group were administered the 2.5 mg apixaban dose. To be enrolled in the ARISTOTLE trial, patients needed to have AF and a CHADS₂ score of ≥ 1 . Valvular AF was defined as moderate or severe mitral stenosis or prosthetic valve. Patients were also excluded for using aspirin at a dose of >165 mg daily or the needed for dual anti-platelet therapy [18].

Dabigatran	75 mg BID dose is indicated for a CrCl 15-30 ml/min
Rivaroxaban	15 mg dose is indicated for a CrCl 30-49 ml/min
Apixaban	2.5 mg BID dose is indicated if 2 or more of the following are present: <ul style="list-style-type: none"> ● Age ≥ 80 ● Body weight ≤ 60 kg ● Serum Creatinine ≥ 1.5 mg/dL
Edoxaban	50% dose reduction for any 1 of the following: <ul style="list-style-type: none"> ● CrCl 30-50 ml/min, ● Body weight ≤ 60 kg ● Concomitant use of verapamil, quinidine or dronedarone

Table 4. Criteria for Anticoagulant Dose Reduction

Clinical outcomes

The primary outcome occurred in 1.27% per year in the apixaban group as compared to 1.60% per year in the warfarin group (HR 0.79; $P < 0.001$ for no inferiority and $P = 0.01$ for superiority) indicating that apixaban was superior to warfarin in preventing stroke or systemic embolism. The rate of hemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group ($P < 0.001$) while there was no significant difference in the rate of ischemic stroke between the two groups. Fatal or disabling strokes occurred at a rate of 0.50% per year in the apixaban group as compared with 0.71% per year in the warfarin group (HR 0.71; $P < 0.05$). The rate of all-cause mortality was lower in the apixaban group than in the warfarin group (3.52% per year vs. 3.94% per year, $P = 0.047$). Fewer patients in the apixa-

ban group than in the warfarin group discontinued the study drug before the end of the study (25.3% vs. 27.5%, $P = 0.01$).

Bleeding and adverse events

Major bleeding, as defined by ISTH criteria [44], occurred at a rate of 2.13% per year in the apixaban group as compared with 3.09% per year in the warfarin group (HR 0.69; $P < 0.001$). The rate of intracranial hemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR 0.42; $P < 0.001$) and the rate of any bleeding was 25.8% per year in the warfarin group and 18.1% per year in the apixaban group, an absolute reduction of 7.7% ($P < 0.001$). There was no significant difference in the rate of gastrointestinal bleeding between the two groups. There appeared to be an even greater reduction in the rate of serious bleeding as defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for severe bleeding and according to the Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding (all P -values < 0.001). Adverse events occurred in essentially equal proportions of patients in the apixaban group and in the warfarin group (81.5% of the patients in the apixaban group and 83.1% of patients in the warfarin group), as did serious adverse events (35.0% and 36.5% in the two groups, respectively) [18].

Discussion

Apixaban, reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31% and death by 11%, but with a lower risk of bleeding and lower rates of discontinuation when compared to warfarin [18]. For every 1000 patients treated for 1.8 years with apixaban instead of warfarin, 6 strokes, 15 major bleeding episodes and 8 deaths were prevented. The improvement in stroke prevention was driven by the prevention of hemorrhagic stroke [18]. For patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding and decreased mortality [18]. This was the first clinical trial to demonstrate a significant reduction in mortality for a NOA over warfarin.

Edoxaban and the ENGAGE AF-TIMI 48 trial

Edoxaban is an oral direct FXa inhibitor that has recently been studied in the ENGAGE AF-TIMI 48 for the prevention of stroke in AF [19, 45]. Edoxaban has 62% oral bioavailability, a peak plasma concentration within 1 to 2 hours and 50% renal excretion (Table 1) [46]. The ENGAGE AF-TIMI 48 trial compared two doses (60 mg or 30 mg) of once-daily edoxaban against warfarin in patients with AF who were at moderate-to-high risk for stroke. Eligible adult patients had AF and a CHADS₂ score ≥ 2 . Important exclusion criteria included an estimated creatinine clearance < 30 ml/min, the use of dual antiplatelet therapy, moderate-to-severe mitral stenosis ("valvular atrial fibrillation"), stroke within 30 days or other indications for anticoagulation therapy [47]. Patients were randomly assigned, in a 1:1:1 ratio, to receive warfarin, 60 mg edoxaban (high dose) or 30 mg edoxaban (low dose). For patients in either edoxaban group, the dose was halved if the patient had any of the following characteristics: estimated creatinine clearance of 30 - 50 ml/min, a body

weight of ≤ 60 kg or the concomitant use of potent P-glycoprotein inhibitors like verapamil, dronedarone or quinidine.

Clinical outcomes

During the study, stroke or systemic embolism (primary outcome) occurred at a rate of 1.50% per year in the warfarin group compared to a rate of 1.18% per year in the 60 mg edoxaban group ($P < 0.001$ for noninferiority) and a rate of 1.61% per year in the 30 mg edoxaban group ($P = 0.005$ for noninferiority). The annual rate of hemorrhagic stroke was 0.47% with warfarin, compared to 0.26% with 60 mg edoxaban and 0.16% with 30 mg edoxaban (both $P < 0.001$). The rate of ischemic stroke was identical (1.25%) with warfarin and 60 mg edoxaban while the rate was increased (1.77%) with 30 mg edoxaban ($P < 0.001$).

There were three prespecified secondary composite outcomes looking at various combinations of stroke, death, cardiovascular death and major adverse cardiac events. These composite outcomes were all significantly lower with the 60 mg edoxaban dose while there was no difference between the 30 mg edoxaban dose and warfarin in the rates of those outcomes. Treatment with both doses of edoxaban was associated with decreased annual rates of cardiovascular death compared with warfarin (3.17% for warfarin vs. 2.74%/2.71% for 60/30 mg edoxaban, $P \leq 0.01$). When all-cause mortality was assessed, 60 mg edoxaban showed a trend towards a mortality benefit over warfarin (4.35% vs. 3.99%, $P = 0.08$), while the 30 mg edoxaban dose did show a reduction in death from any cause (3.8%, $P = 0.006$). A head to head comparison of high-dose and low-dose edoxaban revealed that the rate of stroke was lower with the 60 mg edoxaban dose compared with the 30 mg edoxaban dose ($P < 0.001$). The difference was the result of a 29% relative reduction in the incidence of ischemic stroke with 60 mg edoxaban, which more than counterbalanced a higher incidence of hemorrhagic stroke. The 30 mg edoxaban dose was associated with significantly lower rates of all categories of bleeding compared to the 60 mg edoxaban dose. Given the differences in stroke and bleeding rates, there were no significant differences between the two edoxaban groups with respect to cardiovascular mortality or overall mortality.

Bleeding and adverse events

The annual rate of major bleeding events was lower with both doses of edoxaban (2.75% for 60 mg, 1.61% for 30 mg) compared with warfarin (3.43%, $P < 0.001$). The rates of life-threatening bleeding, intracranial bleeding and major bleeding plus clinically relevant nonmajor bleeding were higher for warfarin compared with either dose of edoxaban ($P < 0.001$). However, the annual rate of major gastrointestinal bleeding was higher with 60 mg edoxaban than with warfarin (1.51% vs. 1.23%), but the rate was lower with 30 mg edoxaban (0.82%).

Discussion

In the ENGAGE AF-TIMI 48 trial, both edoxaban regimens were noninferior to warfarin for the prevention of stroke or systemic embolism but had lower rates of bleeding and cardiovascular death. The 60 mg dose was generally more effective than warfarin. While the rate of ischemic stroke was similar between the two groups, the incidence of

hemorrhagic stroke and the rate of death from cardiovascular causes were significantly lower with the 60 mg edoxaban dose. Edoxaban (60 mg) was consistently associated with lower rates of all forms of bleeding with the exception of gastrointestinal bleeding. Net clinical outcomes (composites of cardiovascular events, death from any cause, bleeding) were lower with 60 mg edoxaban compared to warfarin. The 30 mg dose showed a higher risk of ischemic stroke than warfarin, but there was less hemorrhagic stroke and death from cardiovascular causes compared to warfarin. All forms of bleeding were significantly lower with the 30 mg edoxaban dose including gastrointestinal bleeding than with warfarin. As with the 60 mg dose, the 30 mg dose had lower rates of the net clinical outcomes compared to warfarin. The rate of myocardial infarction was similar between edoxaban and warfarin.

Practical application of the novel oral anticoagulant atrial fibrillation trials

Since October 2010, three new anticoagulants have become available for use in patients with AF with low potential for food and drug interactions, predictable anticoagulant effects and lack of routine monitoring requirements. Clinicians should be familiar with the potential applications of each NOA in order to facilitate a conversation that will allow the patient to make an informed decision.

The most important first step is to know who is and is not appropriate for NOAs. Table 2 outlines common and unique exclusion criteria used in the trials. Many of these exclusion criteria are common sense and apply to all forms of anticoagulation. It is important to understand when to use a reduced dose of a NOA and what the cuts off are for not using a specific NOA. For example, dabigatran and rivaroxaban were not studied at a creatinine clearance (CrCl) < 30 ml/min and apixaban was not studied at a CrCl < 25 ml/min. However, the FDA has approved dabigatran 75 mg twice daily specifically for patients with a CrCl of 15-30 ml/min. Therefore, dabigatran is the only NOA which is approved for use in patients with a CrCl of 15-24 ml/min. None of the NOAs are approved for use in ESRD patients and warfarin is the only appropriate anticoagulant for these patients.

Since NOAs are specifically approved for nonvalvular AF, there is often a question among prescribers as to whether or not their patient has valvular or nonvalvular AF. Valvular heart disease is a common contributor to AF but is often present to varying degrees even when the primary etiology of AF is not related to the valve. Mechanical heart valves were excluded from these trials and one trial comparing dabigatran to warfarin in patients with mechanical valves showed that dabigatran was associated with an increased risk of thromboembolic events and bleeding complications [48]. Therefore, current data only support the use of warfarin in patients with mechanical valves. Bioprosthetic valves are less thrombogenic and may not require anticoagulation. However, current ACCP guidelines do recommend that for patients with a bioprosthetic valve in the mitral position, VKA therapy (target INR, 2.5; range, 2.0-3.0) be used for the first 3 months after valve insertion (Grade 2C) [49]. Therefore, AF in the presence of a properly functioning bio prosthetic valve should not be considered valvular AF, mak-

ing these patients eligible for consideration for NOA therapy.

The RE-LY trial used the definition “hemodynamically relevant valve disease” to define valvular AF. Based on this definition, patients with severe disease of any valve, with either stenosis or insufficiency would be considered to have valvular AF and were therefore excluded. There is a practical explanation for this definition. The RE-LY trial outcomes were all based on an intention-to-treat analysis which meant that once a patient was randomized to a therapy, their outcome would be linked to that therapy regardless of adherence, thus introducing bias in the results. Patients with severe valve disease would be more likely to undergo invasive procedures to correct their valve disease which would artificially increase certain endpoints like stroke, death, bleeding and medication discontinuation rates. If patients were declined intervention for their valve disease, this would also artificially increase morbidity and mortality. Subsequent trials more narrowly defined valvular AF to moderate or severe mitral stenosis implying that aortic stenosis and any form of valvular insufficiency were not types of valvular AF. Again, the concern for introducing bias within the intention-to-treat analysis is a major reason for the exclusion of certain patients with valvular heart disease. The distinction of valvular versus nonvalvular AF appears to be a somewhat artificial distinction that was used to help homogenize the patient populations and exclude patients that were likely to need more interventions that carry significant morbidity and mortality. Since the purpose of VKAs and NOAs are to reduce the formation of thrombus which is thought to be related to a lower flow state within the atria, it does not seem that the presence or absence of valvular heart disease would have much effect on an anticoagulant’s ability to inhibit the thrombotic cascade. There is no theoretical or empiric evidence to suggest that the left atrial thrombotic process is different in valvular heart disease such that warfarin would offer some superiority over NOAs. In our practice, patients with valvular heart disease are considered for NOAs independent of our short or long-term management plans for their valvular heart disease.

The inclusion criteria for each trial were generally based on the use of the CHADS₂ score. There were some minor differences between trials with respect to the definition of heart failure as outlined in Table 2. None of the trials specifically used the newer CHA₂DS₂-VASc scoring system which has been argued to better risk stratify patients, specifically those at lower risk [50]. In the AVERROES trial, peripheral artery disease was considered a risk factor (as it is in the CHA₂DS₂-VASc scoring system) and the RE-LY trial included coronary artery disease (CAD) in conjunction with age 65-74 as a risk factor. In RE-LY, a 65 year old patient with CAD would be randomized to warfarin or dabigatran while the traditional CHADS₂ score would be zero and therefore, based on current practice guidelines, suggest aspirin as a therapeutic alternative. A discussion of the differences and relative merits between CHADS₂ and CHA₂DS₂-VASc is beyond the scope of this review but should be kept in mind when choosing the right anticoagulant for a given patient. In general, the CHA₂DS₂-VASc scoring system is biased in favor of starting a patient on anticoagulation over aspirin therapy. Regardless of whether CHA₂DS₂-VASc is true-

ly better for risk stratifying AF patients, its use will place more lower risk patients on NOAs than the inclusion criteria used in the NOA clinical trials discussed above. Therefore, the information gleaned from these trials about prevention of primary and secondary outcomes as well as bleeding risk do not necessarily apply to patients with borderline risk. It is likely that some patients characterized as appropriate for anticoagulation by CHA₂DS₂-VASc will have a lower risk of stroke and bleeding than patients that were included in the NOA trials and therefore, certain observed benefits of NOAs compared to warfarin will be diminished. From a practical standpoint, if the patient will be better served by being anticoagulated, regardless of risk stratification tool, the use of NOAs should be considered.

Unfortunately, there are no head to head trials directly comparing NOAs. However, we can use the data from the existing AF trials to try and infer which NOA may be best for an individual patient. All of the NOAs appear to be as good as or better than warfarin for the prevention of stroke. Even if statistical significance for superiority was not met (rivaroxaban and 60 mg edoxaban), there was a clear trend towards benefit. Additionally, these medications do not appear to carry an excessive risk of major bleeding relative to warfarin. A recent meta-analysis, which included data from all four NOAs studied in AF, showed that NOAs had a favorable risk-benefit profile with significant reductions in stroke, intracranial hemorrhage, and mortality, with a similar risk of major bleeding compared to warfarin, but increased an increased risk of gastrointestinal bleeding [51]. There are several commonly encountered issues in clinical practice that may favor prescribing one particular NOA over another.

Perhaps the most practical issue is cost since insurance regulations may limit the physician’s choice of NOA. Patients themselves may have personally held beliefs about which NOA will be right for them and this preference should be strongly considered. Many patients like the idea of once daily dosing regimens over twice daily regimens and rivaroxaban (and eventually edoxaban) offer them once daily dosing. Patients who like the idea of once daily dosing should be made aware of the slightly longer half-life of once daily medications and that if bleeding were to occur, it could persist longer due to this increased half-life. It is important that patients take rivaroxaban with food as this increases the bioavailability of the drug [32]. Many AF patients take twice daily medications so this dosing regimen may not be as relevant for some patients.

In patients with renal dysfunction, there are no ideal options. 80% of dabigatran elimination is by the kidneys while rivaroxaban and apixaban only have 66% and 25% renal excretion, respectively. None of the NOAs are recommended for dialysis patients. Dabigatran 75 mg twice daily is the appropriate for dosing regimen for patients with a CrCl 15-30 ml/min, but was not actually studied in the RE-LY trial. The renal cutoff for rivaroxaban is CrCl 30 ml/min. The cutoff for apixaban is CrCl 25 ml/min or serum creatinine >2.5 mg/dL. Since there were so few patients with renal dysfunction in the trials and changes in renal function can lead to supratherapeutic levels of NOAs [33], it may be wise to withhold the use of NOAs in patients with renal dysfunction until more data is available. It

should be noted that renal dysfunction also complicates warfarin therapy and increases the risk of stroke and hemorrhagic complications [52]. In patients with renal dysfunction who are prescribed NOAs, twice daily dosing may be preferable to NOAs with longer half-lives, but this is an unproven hypothesis. Apixaban has twice daily dosing and appears to have the best safety profile without compromising efficacy. Once the CrCl is 15-24 ml/min, dabigatran is the only viable NOA option.

Many patients with AF also have CAD. The RE-LY trial showed an apparent increase in the rate of MI compared to warfarin. This begs the question of whether dabigatran causes MI or if warfarin, which inhibits thrombin, FXa, factor VIIa and factor IXa, is simply more protective against MI. The other three NOAs, which are all direct FXa inhibitors did not show an increased risk of MI compared to warfarin [16-19]. Additionally, other studies looking at FXa inhibition in CAD and MI have found better outcomes in patients taking FXa inhibitors [53, 54]. Interestingly, a prior study with an earlier generation direct thrombin inhibitor, ximelagatran, did not show an increased risk of MI relative to warfarin [55]. However, a recent meta-analysis indicates that patients taking DTIs were more likely to have an MI than patients taking warfarin (odds ratio 1.35, $P=0.005$) [56]. Additionally, there was no evidence of warfarin being more protective against MI when compared to FXa inhibitors, aspirin or clopidogrel. Therefore, the increased MI risk appears to be a class effect specific to any DTI and not a specific phenomenon unique to dabigatran or a protective effect of warfarin [56].

Another consideration is that patients with CAD are also taking aspirin, thienopyridines or dual antiplatelet therapy (DAPT). DAPT was not an exclusion from RE-LY trial but it was from every other AF trial. Obviously, the combination of antiplatelet agents with anticoagulants will increase the risk of bleeding regardless of NOA chosen. The lowest possible dose of aspirin should be used and patients should only be on DAPT and anticoagulation (triple therapy) for as brief a time as possible. Therefore, in patients with a history of CAD or MI, it may be preferable to treat the patient with a direct FXa inhibitor. However, it is important to remember that despite an increased risk of MI with dabigatran relative to warfarin, this does not mean that dabigatran has an increased risk of MI relative to the other NOAs. Furthermore, patients on dabigatran in the RE-LY trial were less likely to die than patients on warfarin (All-cause mortality RR 0.88; $P=0.051$).

For patients with AF who have had a prior stroke, further stroke prevention is of paramount importance. Based on the design of these trials which made stroke prevention the primary outcome, the strongest recommendations about NOA use can be made with respect to stroke prevention. As noted earlier, no trials exist which compare different NOAs head to head. With respect all-cause stroke, dabigatran and apixaban were superior to warfarin, while rivaroxaban and edoxaban were noninferior. However, only dabigatran was superior in preventing ischemic stroke while apixaban's overall superiority was driven by its impressively lower risk of hemorrhagic stroke. However, apixaban was not better than warfarin in preventing ischemic stroke.

All four NOAs carry a decreased risk of intracranial bleeding, which can be argued to be the single greatest advantage of using NOAs over VKAs as intracranial hemorrhage is generally the most devastating complication of anticoagulation therapy. If risk of bleeding is the biggest concern, then apixaban is likely to be the most appropriate agent to prescribe. Based on the AVERROES and ARISTOTLE data, apixaban is superior in preventing stroke, improves mortality and appears to be just as safe as aspirin (and clearly safer than warfarin). Patients with a history of gastrointestinal bleeding (GIB) should be considered for apixaban since dabigatran, rivaroxaban and 60 mg edoxaban increase the risk of GIB.

Some patients will have other pro-thrombotic conditions in addition to AF. Although one would expect that all of the NOAs would be able to address any thrombotic condition, to-date, only rivaroxaban carries FDA approved indications beyond AF. These include treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), for the reduction in the risk of recurrence of DVT and of PE following an initial 6 months of treatment for DVT and/or PE as well as DVT prophylaxis after knee or hip replacement surgery [35-37]. For patients with documented or suspected hereditary or acquired thrombophilias, it is not known if NOAs are an acceptable alternative to warfarin or heparin. Expert consultation with a hematologist is advised for these patients.

In patients deemed unsuitable for warfarin due to documented or expected intolerance to warfarin, the data very clearly supports the use of apixaban over aspirin. As stated above, the data show that apixaban is better than warfarin and just as safe as aspirin. Based on the AVERROES data, it is very difficult to justify the use of aspirin in warfarin-contraindicated AF patients over apixaban. The one obvious exception is cost. Although no formal cost-benefit analysis has been done, it is plausible that the long term costs associated with the increased risk of stroke while on aspirin would be greater than the cost of using apixaban.

As outlined above, the decision to start a patient on an NOA can be a complicated one with numerous factors to consider. Fortunately, patients now have options other than warfarin that are well-validated by large scale clinical trials to help guide the decision making process. Although the data for NOAs is far from complete, there does appear to be an adequate amount of data to allow the clinician and the patient to make an informed decision about anticoagulation in AF. As new data and studies emerge, the above recommendations should be interpreted in the context of this new information. Practicing clinicians should expect the field of anticoagulation to be a dynamic and rapidly changing one over the next decade.

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