

Clinical trials update: recent and ongoing studies in anticoagulation for atrial fibrillation

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Abstract: Atrial fibrillation is the most common sustained cardiac arrhythmia in the adult population, with a marked increased risk associated with age. Perhaps the most devastating complications of atrial fibrillation include acute ischemic stroke or systemic embolization. Vitamin K antagonists such as warfarin have served as the primary pharmacologic agent for the prevention of these thrombotic complications. Despite the widespread use of vitamin K antagonists, their effectiveness is hindered by several factors, including delayed onset of action, multiple food and drug interactions, onerous monitoring and dosing regimens, and a narrow therapeutic window. To address these limitations, multiple novel oral anticoagulants targeting thrombin or factor Xa have progressed through clinical development or received regulatory approval for clinical use in recent years. These agents offer the potential for enhanced efficacy, as well as an improved safety profile. Here, the phase II and III clinical trial data detailing the potential risks and benefits of these agents are reviewed.

Keywords: atrial fibrillation, factor Xa inhibitor, direct thrombin inhibitor, clinical trial

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, with a lifetime risk of nearly 25% in adults.¹ The risk of stroke is markedly elevated from 1% to 20% annually among adults with nonvalvular AF.² AF is also associated with increased in-hospital mortality in both atherothrombotic and cardioembolic stroke patients.³ Vitamin K antagonists (VKAs) have been the primary pharmacologic therapy for the prevention of thrombotic complications in patients with AF for decades.⁴ Treatment with a VKA has a class I recommendation for all patients with nonvalvular AF who are at elevated risk of stroke or systemic embolization.⁴ These recommendations are supported by an observed reduction of up to 62% in the risk of stroke in patients with nonvalvular AF treated with VKAs.⁵

Despite their effectiveness in the prevention of thrombotic complications in patients with AF, VKAs are underutilized, and in clinical practice they may be relatively ineffective in these patients.^{6,7} This observation has been attributed to several factors intrinsic to VKAs, including a delayed onset of anticoagulant effect, narrow therapeutic window, early prothrombotic effect observed with therapy initiation, burdensome drug monitoring including frequent laboratory testing, and unpredictable anticoagulant effects secondary to numerous medication and food interactions and genetic polymorphisms.⁸

To address the limitations and complexities associated with VKAs, in recent years multiple novel oral anticoagulants, including those targeting thrombin or factor

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Xa directly, have progressed through clinical development or received regulatory approval in this patient population and entered into clinical practice. In particular, dabigatran (Pradaxa; Boehringer Ingelheim Pharmaceuticals, Ingelheim, Germany), apixaban (Eliquis; Bristol-Myers Squibb, New York, NY, USA), and rivaroxaban (Xarelto; Johnson and Johnson, New Brunswick, NJ, USA, and Bayer Schering Pharma, Berlin, Germany) were recently approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with nonvalvular AF.

These agents have been evaluated in three major clinical trials comparing warfarin to the respective novel anticoagulant in patients with nonvalvular AF⁹⁻¹¹ (Table 1), as well as one comparing acetylsalicylic acid to apixaban in patients for whom warfarin was deemed unsuitable.¹² In addition to these agents, two other factor Xa inhibitors – betrixaban (Portola Pharmaceuticals, San Francisco, CA, USA) and edoxaban (Lixiana; Daiichi Sankyo, Tokyo, Japan) have reached late stages of clinical development and been investigated in phase II randomized, controlled trials.^{13,14} Here, the key aspects of the pivotal trials for each of these agents are reviewed.

Direct thrombin inhibitors

Dabigatran

Dabigatran etexilate is an oral, direct thrombin inhibitor recently approved for use in patients with nonvalvular AF. This medication is supplied as a prodrug, and after ingestion is quickly converted to its active metabolite.¹⁵ Peak plasma concentrations are observed in approximately 2–3 hours, and this agent has a half-life of 12–14 hours (Table 2). Nearly 80% of ingested dabigatran is eliminated via the renal system, while the other 20% is conjugated and excreted via

the biliary system. Dabigatran does not interact with hepatic cytochrome P450 (CYP) enzymes. It does, however, interact with the efflux transporter P-glycoprotein (P-gp),¹⁶ and is therefore subject to drug interactions with agents that activate (eg, rifampin) or inhibit (eg, amiodarone, ketoconazole, quinidine, or verapamil) this transporter.

The use of dabigatran in patients with nonvalvular AF was investigated in the phase III RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial.¹¹ In RE-LY, 18,113 patients were randomized in a prospective, randomized, open-label, blinded end-point (PROBE) design to either 110 mg or 150 mg of dabigatran twice daily or open-label warfarin (target international normalized ratio [INR] 2.0–3.0). The median follow-up was 2 years. At the end of this follow-up, no significant difference was observed in the primary efficacy end point (composite of stroke or systemic embolism) between those treated with warfarin compared to those treated with 110 mg dabigatran (1.69% versus [vs] 1.53% per year, $P < 0.001$ for noninferiority). However, the rate of the primary efficacy end point was significantly lower in the 150 mg group compared to the warfarin group (1.11% vs 1.69% per year, $P < 0.001$ for noninferiority and superiority). The rate of major bleeding was lower with lower-dose dabigatran compared to warfarin (2.71% vs 3.36% per year, $P = 0.003$), and similar between the 150 mg dose group and warfarin-treated patients (3.11% vs 3.36% per year, $P = 0.31$). The risk of life-threatening bleeding was significantly lower with both doses of dabigatran compared to warfarin (1.22% and 1.45% vs 1.80%, $P < 0.05$ for all comparisons of dabigatran to warfarin). The rate of intracranial hemorrhage was also significantly reduced for each dabigatran dose group relative to warfarin-treated patients (0.23% and 0.30% for the 110 mg and 150 mg dose groups,

Table 1 Phase III trials of novel anticoagulants in nonvalvular atrial fibrillation

	RE-LY	ROCKET AF	ARISTOTLE	EngageAFTIMI48
Medication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg)	150 and 110 mg twice daily	20 or 15 mg* daily	5 or 2.5 mg** twice daily	30 and 60 mg daily
n	18,113	14,264	18,201	>21,000
Design	PROBE	Double-blind	Double-blind	Double-blind
AF criteria	AF × 1	AF × 2	AF or AF × 2	AF × 1
	<6 months	≥1 in <30 days	<12 months	<12 months
% VKA-naive	50	38	43	40 (goal)
CHADS ₂ (median)	2.2 (mean)	3.5	2.1	NA
CHADS ₂ 3–6 (%)	32.5	87	30.2	NA

Notes: *Dose reduced to 15 mg in patients with creatinine clearance of 30–49 mL/minute; **dose reduced to 2.5 mg in patients with reduced drug clearance.

Abbreviations: RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Non-valvular Atrial Fibrillation; ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation; EngageAFTIMI48, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation; PROBE, prospective, randomized, open-label, blinded end-point evaluation; AF, atrial fibrillation; VKA, vitamin K antagonist; NA, not available.

Table 2 Characteristics of novel anticoagulants

Drug name	Dabigatran	Apixaban	Rivaroxaban	Betrixaban	Edoxaban
Target	Factor IIa (thrombin)	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Dosing	Twice daily	Twice daily	Daily	Daily	Once or twice daily
Half-life (hours)	12–14	8–13	5–13	19	6–11
Renal excretion (%)	80	25	66	17	35
Drug interactions	Potent inhibitors/ inducers of P-gp	Potent inhibitors of CYP3A4	Potent inhibitors of CYP3A4 or inhibitors/ inducers of P-gp	Low potential reported	Potent inhibitors of CYP3A4 or inhibitors/ inducers of P-gp
Routine coagulation monitoring	None	None	None	None	None

Abbreviations: P-gp, P-glycoprotein; CYP3A4, cytochrome P450 3A4.

respectively, vs 0.74%; $P < 0.05$ for both dabigatran-dose groups compared to warfarin).

Despite similar efficacy and an enhanced safety profile for dabigatran, warfarin demonstrated superior tolerability relative to dabigatran. A total of 15% and 21% of patients receiving 110 mg dabigatran discontinued use by the end of the first and second years, respectively. A similar proportion of patients, 16% and 21%, receiving 150 mg dabigatran discontinued the study medication at 1 and 2 years, respectively, compared to discontinuation rates of 10% at 1 year and 17% at 2 years in warfarin-treated patients ($P < 0.001$). This difference was attributed to higher rates of dyspepsia with dabigatran compared to warfarin (11.8% and 11.3% for the 110 mg and 150 mg groups, respectively, vs 5.8% for warfarin; $P < 0.001$ for both comparisons).

Direct factor Xa inhibitors Apixaban

Apixaban is an oral, direct, reversible inhibitor of factor Xa that after ingestion reaches peak plasma concentrations between 1 and 3 hours (Table 2).¹⁵ The observed half-life of apixaban is 8–13 hours. In addition, apixaban is predominantly metabolized via the liver, and approximately 25% of drug is excreted renally.

Apixaban was evaluated in patients with nonvalvular AF in the phase III AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double Blind Trial) trial.¹² In AVERROES, 5,599 patients with nonvalvular AF as well as at least one risk factor for ischemic stroke, and who were considered “unsuitable” for VKA therapy, were randomized in a prospective, double-blinded fashion to either apixaban 5 mg twice daily or aspirin therapy. The mean follow-up was roughly 1 year. In AVERROES, the rate of stroke or systemic embolism was significantly

reduced in apixaban-treated patients compared to aspirin-treated patients (1.65% vs 3.7% per year, hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.32–0.62; $P < 0.001$). A nonsignificant reduction in mortality was also observed with apixaban therapy relative to the aspirin control group (3.5% vs 4.4% per year, HR 0.79, 95% CI 0.62–1.02; $P = 0.07$). In addition, the risk of first cardiovascular hospitalization was significantly reduced in apixaban-treated patients compared to those receiving aspirin (12.6% vs 15.9% per year, $P < 0.001$). Finally, treatment with apixaban was associated with a similar risk of major bleeding (1.4% vs, 1.2% per year, HR 1.13, 95% CI 0.74–1.75; $P = 0.57$) as well as intracranial bleeding (0.4% vs 0.4%, HR 0.85, 95% CI 0.38–1.90; $P = 0.69$) compared to aspirin.

Apixaban was also investigated and compared directly to standard warfarin therapy in the phase III ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trial.⁹ In ARISTOTLE, 18,201 patients with AF and at least one risk factor for thromboembolism were randomized to either apixaban 5 mg twice daily or warfarin (goal INR 2–3). Both prescribers and patients were blinded to treatment. The median follow-up was 1.8 years, after which the rate of the primary efficacy end point (a composite of stroke or systemic embolism) was reduced in apixaban-treated patients compared to those treated with warfarin (1.27% vs 1.60% per year, HR 0.79, 95% CI 0.66–0.95; $P < 0.001$ for noninferiority, $P = 0.01$ for superiority). In addition, apixaban demonstrated an enhanced safety profile compared to warfarin, as the rate of major bleeding (2.13% vs 3.09%, HR 0.69, 95% CI 0.60–0.80; $P < 0.001$) as well as the rate of all-cause mortality were significantly reduced with apixaban compared to warfarin (3.52% vs 3.94%, HR 0.89; 95% CI 0.80–0.99; $P < 0.047$). A 58% relative risk reduction in the risk of intracranial hemorrhage was also observed with apixaban compared to treatment with warfarin (0.33% vs 0.80% per year, HR 0.42, 95% CI 0.30–0.58; $P < 0.001$).

Rivaroxaban

Rivaroxaban is another oral, reversible, direct-acting factor Xa inhibitor that has recently received regulatory approval for the prevention of stroke or systemic embolization in patients with nonvalvular AF. Similar to apixaban, rivaroxaban is rapidly absorbed upon ingestion and reaches peak plasma concentrations in 2–4 hours (Table 2).¹⁷ The half-life of rivaroxaban is 5–13 hours.¹⁵ In addition, rivaroxaban is initially metabolized in the liver and subsequently excreted by both renal and fecal routes. Approximately two-thirds of the ingested dose is metabolized via hepatic CYP450 enzymes.^{17–19} Fifty percent of these metabolites are excreted via the kidneys, with the rest eliminated in the feces. Additionally, one-third of the ingested rivaroxaban dose is excreted renally as unmodified active drug.

The role of rivaroxaban for anticoagulation in patients with non-valvular AF was explored in the phase III ROCKET AF (Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Non-valvular Atrial Fibrillation) trial.¹⁰ In ROCKET AF, 14,264 patients with a CHADS₂ score of 2 or greater were randomized to either rivaroxaban 20 mg daily or warfarin (target INR 2–3). The dose of rivaroxaban was reduced to 15 mg daily in patients with creatinine clearance of 30–49 mL/minute. Both prescribers and patients were blinded to treatment. The median follow-up was 1.9 years, after which the rate of stroke and non-central nervous system thromboembolism was reduced with rivaroxaban compared to warfarin (1.7% vs 2.2% per year, HR 0.79, 95% CI 0.66–0.96; $P < 0.001$ for noninferiority). In the intention-to-treat analysis, treatment with rivaroxaban was noninferior to warfarin therapy for the prevention of stroke (2.1% vs 2.4%, HR 0.88, 95% CI 0.74–1.03; $P < 0.001$ for noninferiority, $P = 0.12$ for superiority). Additionally, the rate of major and clinically relevant nonmajor (CRNM) bleeding was similar between rivaroxaban and warfarin (14.9% vs 14.5%, HR 1.03, 95% CI 0.96–1.11; $P = 0.44$). Of note, relative to warfarin-treated patients, rivaroxaban treatment was associated with a 33% relative reduction in the risk of intracranial hemorrhage (HR 0.67, 95% CI 0.31–0.79; $P = 0.003$) and a 50% relative risk reduction in the risk of fatal bleeding (HR 0.50; 95% CI 0.31–0.79; $P = 0.003$). In addition, a planned secondary analysis found the treatment effect of warfarin was consistent across dosing groups based on renal function, indicating the dose reduction to 15 mg daily in this patient population was equally safe and effective.²⁰

Betrixaban

Betrixaban is an oral, direct factor Xa inhibitor with a half-life of approximately 19 hours (Table 2).¹⁵ It is rapidly absorbed, reaching peak plasma concentrations in 3–4 hours after administration.¹⁴ Oral bioavailability is approximately 34% and protein binding roughly 60%. Betrixaban is primarily excreted unchanged via the biliary system; however, approximately 17% is excreted via the kidneys.

Betrixaban was studied in patients with nonvalvular AF in the EXPLORE-Xa (Phase 2 Study of the Safety, Tolerability and Pilot Efficacy of Oral Factor Xa Inhibitor Betrixaban Compared to Warfarin) trial.¹⁴ EXPLORE-Xa was a dose-ranging study in which 508 patients were randomized to receive 40, 60, or 80 mg once daily or unblended warfarin with a target INR of 2.0–3.0. The primary outcome was the time to occurrence of major or CRNM bleeding. The secondary outcomes included any bleeding (major, CRNM, and any other reported bleeding), as well as time to occurrence of death, ischemic or nonischemic stroke, myocardial infarction (MI), or other systemic embolism.

Patients were randomized in a 1:1:1:1 allocation to betrixaban 40, 60, or 80 mg orally, once daily, or warfarin. Randomization to betrixaban or warfarin was not blinded, but the betrixaban dose was double-blinded. Subjects were assessed at screening, and at weeks 0, 1, 2, 4, 8, and 12, and then every 2 months thereafter for a minimum of 90 days and a maximum of 1 year.

The rates of the primary outcome were lowest in the betrixaban 40 mg group (HR 0.14 vs warfarin, P -value unadjusted for multiple testing = 0.04, 95% CI 0.017–1.135). The betrixaban 60 mg and 80 mg daily groups had rates similar to warfarin. The rates of any bleeding were significantly less for betrixaban 40 mg and 80 mg compared with warfarin (95% CI 0.301–0.856 for 40 mg vs warfarin and 0.332–0.914 for 80 mg vs warfarin; $P = 0.01$ and 0.02, respectively).

There was one ischemic stroke in the betrixaban 60 mg and 80 mg groups and none in the betrixaban 40 mg or warfarin groups. There were two deaths, both vascular: one in the betrixaban 40 mg group and one in the warfarin group. There were no MIs, systemic embolic events, or pulmonary embolism events during the study. Similar rates of serious adverse events were observed across all groups (9.4%, 9.4%, 8.7%, and 0.4% for betrixaban 40 mg, 60 mg, 80 mg, and warfarin groups, respectively). Significantly higher rates of diarrhea were observed for the pooled betrixaban groups compared to the warfarin group (6.0% vs 0.8%), and rates of premature discontinuation for any cause were higher with

betrixaban compared to warfarin (8.9% vs 6.3%). The percentages of patients with elevated alanine aminotransferase greater than three times the upper limit of normal on betrixaban and on warfarin were 1.8% and 0.8%, respectively. No dose-dependent increase in alanine aminotransferase was observed with betrixaban.

Edoxaban

Edoxaban is an oral, direct-acting factor Xa inhibitor with a half-life of 6–11 hours (Table 2).^{21,22} It is rapidly absorbed after ingestion, reaching peak plasma concentrations within 1–2 hours. The oral bioavailability of edoxaban is at least 50%, and approximately 35% is excreted via the kidneys, with the rest excreted in the feces.

Edoxaban has been evaluated in patients with non-valvular AF in the phase III EngageAFTIMI48 (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation) trial (Table 1).²³ Results of this trial are pending at this time; however, phase II has previously been published, providing some insight into the efficacy and safety of this agent in this patient population.¹³

In this dose-ranging, 12-week parallel-group, multicenter, prospective, phase II study, 1,146 patients with nonvalvular atrial fibrillation with a CHADS₂ score of at least 2 and a creatinine clearance greater than 30 mL/minute were randomized in a 1:1:1:1:1 ratio to oral edoxaban 30 mg daily, 30 mg twice daily, 60 mg daily, 60 mg twice daily, or warfarin with a target INR of 2.0–3.0. Participants and investigators were blinded to the edoxaban dose, but warfarin was administered open-label. The primary outcomes were the composite of major and/or CRNM bleeding and elevated hepatic enzymes and/or bilirubin. Stroke and systemic embolization were secondary end points. Of note, only 889 patients completed the study.

Major plus CRNM bleeding occurred in 3.2% of patients randomized to warfarin compared to 3.0% ($P = 1$), 7.8% ($P = 0.029$), 3.8% ($P = 0.807$), and 10.6% ($P = 0.002$) in the edoxaban 30 mg daily, 30 mg twice-daily, 60 mg daily, and 60 mg twice-daily groups. No significant differences were observed in hepatic enzyme or bilirubin elevations between the edoxaban and warfarin groups. The safety profiles of edoxaban 30 mg and 60 mg daily regimens were similar to warfarin, whereas the twice-daily dose regimens were associated with significantly more bleeding. Therefore, only the 30 mg and 60 mg daily dose regimens will be assessed in Engage AFTIMI 48.²³

What can we learn from the clinical trials?

In light of the recent increase in clinical trial data and regulatory approval of novel oral anticoagulants for use in patients with nonvalvular AF, application to clinical practice has become an increasingly germane issue. While betrixaban and edoxaban are currently under development for this clinical application, practical conclusions are difficult to draw for these agents, given their relatively preliminary trial findings. Therefore, this discussion will be limited to those agents that have published phase III data or have received regulatory approval for use in this patient population.

The collective results of the phase III trials with dabigatran, apixaban, and rivaroxaban signify the advent of potentially safer and more efficacious oral anticoagulants. However each of these agents, including warfarin, have distinct pharmacological characteristics that should be considered when contemplating initiating one of these agents. In addition, the clinical trials possess significant variability and nuances that may provide some insights for translation to clinical practice.

While RE-LY, ARISTOTLE, and ROCKET AF provide significant clinical data regarding the use of these novel oral anticoagulants compared to warfarin, the recent regulatory approvals of dabigatran, apixaban, and rivaroxaban present new challenges to clinicians managing patients with AF. In order to make informed decisions when choosing an anticoagulant, clinicians should be aware of several distinct differences in trial design between RE-LY, ARISTOTLE, and ROCKET AF.

While both ARISTOTLE and ROCKET AF were randomized, double-blinded trials, as mentioned previously, RE-LY utilized a PROBE design in which those randomized to warfarin were not blinded to treatment assignment.^{10–12} Although it is difficult to ascertain objectively how this difference may have affected outcomes in the respective trials, clinicians should be aware of several potential sources of bias inherent in the differing trial designs. In open-label trials, central adjudication committees can be utilized to evaluate possible end-point events independent from study sites and blinded to subject treatment allocation. This is a characteristic of a PROBE design, where medications are dispensed in an open-label fashion while end points are adjudicated by a committee blinded to subject allocation, and helps eliminate subjectivity with regard to outcome assessment. Conceivably, an open-label design allows management of intercurrent events based on the specific intrinsic characteristics of the anticoagulant, rather than a broad management for all patients as if they

were on warfarin. This type of management is therefore more likely to represent true differences accurately in the management of warfarin and the comparator anticoagulant in daily practice.²⁴

Generally, a blinded trial is assumed to be less prone to bias than an open-label trial, as blinding limits the effects of knowledge of treatment allocation on postrandomization treatment decisions and outcome reporting.²⁵ However, blinded trials are not always possible, due to cost considerations and complexity in design. In addition, double-blinded trials may introduce other sources of bias in their own right, such as biases in patient selection by excluding patients for whom complicated double-dummy medication regimens are deemed too burdensome. In addition, patient recruitment can be easier in an open-label trial compared to a double-blinded trial, as was observed with RE-LY compared to ROCKET AF. The difference in design between open-label and double-blind trials may also lead to differences in patient populations due to subjective preselection protocols.²⁶

Although the patient populations in RE-LY and ARISTOTLE were quite similar, ROCKET AF was comprised of a significantly higher-risk patient population.²⁷ In ROCKET AF, 87.0% of patients had a CHADS₂ score of 3–6, whereas only 32.5% and 30.2% of patients in RE-LY and ARISTOTLE, respectively, had CHADS₂ scores of 3–6. Also, 54.8% of patients in the ROCKET AF cohort had a prior history of stroke, transient ischemic attack, or systemic embolism compared to 20.0% and 19.4% in RE-LY and ARISTOTLE, respectively. The prevalence of heart failure, hypertension, and diabetes was also higher in the ROCKET AF cohort compared to the patient populations in RE-LY and ARISTOTLE.

The higher-risk patient population studied in ROCKET AF has several implications that should be considered when interpreting the results of the clinical trials involving novel oral anticoagulants. Perhaps not surprisingly, the rate of all-cause mortality was higher in ROCKET AF compared to ARISTOTLE and RE-LY (4.95% per year vs 3.94% and 4.13%, respectively).^{9–11} An increase in the primary efficacy end points was also observed in the control groups in ROCKET AF compared to ARISTOTLE and RE-LY (2.4% per year vs 1.6% and 1.69%, respectively).

In addition, although the time in therapeutic range (TTR) observed with warfarin was lower in ROCKET AF compared to that observed in RE-LY or ARISTOTLE (median TTRs 58%, 67%, and 66%, respectively), this may be a direct result of the patient populations in the individual trials, as TTR decreases with increasing CHADS₂ score.²⁸ In addition, the

presence of individual CHADS₂ components, including heart failure, hypertension, and diabetes, all of which were higher in ROCKET AF compared to RE-LY and ARISTOTLE, are also associated with lower TTR. It should be noted that the effect of rivaroxaban on the primary efficacy end point was consistent across all TTR quartiles, as was the effect on intracranial hemorrhage, although treatment effect was greater in those with lower TTR values.²⁹ However a significant interaction was observed between TTR and major or CRNM bleeding, as well as for major bleeding, with rivaroxaban demonstrating a lower HR with the lowest quartile TTR and a higher HR in centers with the highest TTR.

Patient-specific issues

One major advantage of each of these novel oral anticoagulants is the lack of need for onerous, routine laboratory monitoring and dose titration, as is required for warfarin. In addition, rivaroxaban's once-daily regimen may be preferable over the twice-daily regimens of dabigatran or apixaban for certain patients. However providers should also consider that warfarin's relatively longer half-life may provide more stability of anticoagulation compared to the novel oral anticoagulants in patients for whom medication compliance is an issue due to its longer half-life.

Elderly

The elderly are a subpopulation of patients who may receive the greatest benefit from these novel oral anticoagulants relative to warfarin. In RE-LY, the effects of dabigatran were similar regardless of patient baseline characteristics, including age.¹¹ It should be noted, though, that a subsequent secondary analysis of the data from RE-LY suggested a nominal trend towards more extracranial bleeding in patients age 75 years and older treated with 150 mg dabigatran compared to warfarin therapy.³⁰ Despite this observation, age was not observed to exert an effect on the beneficial outcomes associated with dabigatran relative to warfarin for the risk of intracranial bleeding. Additionally, although the 110 mg dose did not receive regulatory approval by the US FDA, this dose is associated with significantly less major bleeding (4.43% vs 5.10%, $P < 0.001$ for interaction with age) in elderly patients (75 years and older) compared to the 150 mg dose.³⁰ This dose was approved by the European Medicines Agency (EMA), and is the recommended dose in patients 75 years and older, according to the EMA.³¹

Similar to dabigatran, the efficacy of apixaban in elderly patients remained consistent compared with warfarin⁹ and aspirin.¹² In addition, major bleeding was lower with

apixaban compared to warfarin⁹ and similar to that observed with aspirin therapy.¹² Similar efficacy results were reported for rivaroxaban in elderly patients in ROCKET AF, although the overall bleeding rate was increased slightly with rivaroxaban compared to warfarin.^{10,32} It should be noted, however, that the risk–benefit ratio for rivaroxaban was consistently favorable across all age-groups.

Renal dysfunction

Warfarin is primarily excreted through the metabolic enzymatic activity of the liver; however, data exist that suggest dose reductions may be necessary in patients with renal dysfunction.³³ For instance, results from the Pharmacogenetic Optimization of Anticoagulation Therapy cohort indicated that patients with moderate-to-severe renal dysfunction might have decreased dosing requirements with warfarin compared to patients with normal renal function.³⁴ Because patients with end-stage renal disease, including those requiring hemodialysis, were excluded from RE-LY, AVERROES, and ROCKET AF, warfarin remains the drug of choice in this group of patients.

The primary mechanism of excretion of dabigatran is via the renal system.¹⁵ Therefore, this agent should be used with caution in patients with renal dysfunction. Dabigatran is contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 15 mL/minute.⁸ For those with severe renal dysfunction characterized by a creatinine clearance of 15–30 mL/minute, the dose approved by the US FDA is reduced to 75 mg daily.³⁵ This dose was not evaluated in RE-LY, as patients with an estimated eGFR less than <15 mL/minute were excluded from the study.¹¹ Despite these considerations, no significant interactions were reported for either the primary efficacy or safety end points in RE-LY when stratified by renal function, suggesting this agent does indeed remain a viable alternative to warfarin in patients with moderate-to-severe renal dysfunction.¹¹ Of note, the recommended dose according to the EMA in patients with an eGFR between 30 and 50 mL/minute is 110 mg twice daily.³¹

For apixaban, patients with a creatinine clearance of less than 25 mL/minute were excluded from ARISTOTLE.⁹ However, in both ARISTOTLE and AVERROES, the dose was reduced to 2.5 mg twice daily in patients who had evidence of decreased renal clearance.^{36,37} When stratified by renal function, apixaban reduced the rates of stroke, death, and major bleeding compared to warfarin consistently across all levels of renal function.³⁸

Because nearly 66% of an oral rivaroxaban dose is excreted via the renal system (50% as unchanged drug and 50% as inactive metabolites),¹⁵ special dosing considerations

are warranted in patients with decreased creatinine clearance. Patients with an eGFR less than 30 mL/minute were excluded from ROCKET AF.¹⁰ Patients with an eGFR between 30 and 49 mL/minute received a reduced dose of 15 mg daily. Analysis of this patient cohort demonstrated the treatment effect of rivaroxaban was consistent across all dosing groups in ROCKET AF, indicating this reduced dose retains the safety and efficacy profile observed with 20 mg daily in patients with an eGFR between 30 and 40 mL/minute.²⁰

Patients at high risk for bleeding events

One major consideration with oral anticoagulant therapy is the individual patient's bleeding risk. Several distinct models or scoring systems, such as the HAS-BLED scoring system, were established in order to quantify an individual patient's bleeding risk.³⁹ For patients at low or moderate risk of bleeding complications, any of the approved oral anticoagulants may be appropriate for use. However, for the higher-risk patients, the trial data suggest these novel oral anticoagulants may have distinct advantages over warfarin therapy with regard to bleeding outcomes.^{9–11}

In RE-LY, treatment with 150 mg dabigatran was associated with a significantly lower risk of life-threatening bleeding complications (1.45% vs 1.80%, $P < 0.05$),¹¹ as well as the risk of intracranial hemorrhage compared to warfarin (0.30% vs 0.74%, $P < 0.05$). Subsequent analysis demonstrated a number needed to treat of 250 patients to prevent one bleeding event.⁴⁰ In addition, similar reductions were observed with the 110 mg dose of dabigatran for the risk of life-threatening bleeding and intracranial hemorrhage.

Treatment with apixaban also demonstrated an enhanced safety profile with regard to bleeding outcomes compared to warfarin-treated patients.⁹ Compared to warfarin, apixaban was associated with 58% and 31% relative risk reductions in the risk of intracranial hemorrhage and major bleeding, respectively. In addition, apixaban was associated with a 29% relative risk reduction in the risk of any bleeding compared to warfarin-treated patients.

As noted previously, the patient cohort in ROCKET AF was a significantly higher-risk cohort than that of RE-LY or AVERROES.¹⁰ In this high-risk patient population, no significant differences were observed in the rates of major and CRNM bleeding between patients receiving rivaroxaban or warfarin. However, rivaroxaban therapy was associated with significant reductions in fatal bleeding (0.4% vs 0.8%, HR 0.50, 95% CI 0.31–0.79; $P = 0.003$) and intracranial hemorrhage (0.8% vs 1.2%, HR 0.67, 95% CI 0.47–0.93; $P = 0.02$) compared to the warfarin group.

Currently, the data regarding reversibility of anticoagulant effects of these novel oral anticoagulants are limited; however, the available data suggest that factor Xa inhibitors may be “reversible” with blood-replacement products such as prothrombin complex concentrates.⁴¹ These same products do not appear to offer the same “reversibility” with dabigatran. The safety and efficacy of activated prothrombin protein complexes, higher doses of prothrombin complex concentrates, and recombinant factor VII in this setting with dabigatran are currently unknown. It has been suggested that activated charcoal may offer the potential for adsorption of recently ingested (within a few hours) doses of dabigatran.⁴² In addition, hemodialysis may be successful in removing approximately two-thirds of the circulating active metabolite of dabigatran within 2–4 hours.⁴³

Triple-antithrombotic therapy

An increased rate of bleeding complications has been observed in patients with an indication for both dual-antiplatelet therapy (DAPT) and an oral anticoagulant. An analysis of one Danish registry of patients discharged following a first hospitalization for AF found an increased HR for combined fatal and nonfatal bleeding in patients receiving DAPT and warfarin (HR 3.70, 95% CI 2.89–4.76), clopidogrel and warfarin (HR 3.08, 95% CI 2.32–3.91), aspirin and warfarin (HR 1.83, 95% CI 1.72–1.96), and aspirin and clopidogrel (HR 1.66, 95% CI 1.34–2.04) compared to warfarin alone. No elevated risk was observed with aspirin monotherapy (HR 0.93, 95% CI 0.88–0.98) or clopidogrel monotherapy (HR 1.06, 95% CI 0.87–1.29) compared to warfarin monotherapy.⁴⁴

Several novel oral anticoagulants have been investigated in combination with DAPT. In the RE-DEEM (Dose-Finding Study for Dabigatran Etexilate in Patients with Acute Coronary Syndrome) trial, patients with a recent ST-elevation or non-ST-elevation acute coronary syndrome (ACS) were randomized to DAPT and increasing doses of dabigatran or matching placebo.⁴⁵ The addition of dabigatran was associated with a dose-dependent increase in International Society of Thrombosis and Haemostasis-defined major or CRNM bleeding compared to placebo (3.5%, 4.3%, 7.9%, and 7.8% for 50, 75, 110, and 150 mg dabigatran groups, respectively, vs 2.2% for placebo; $P < 0.001$ for trend). In RE-LY, the risk of major bleeding was nearly twice as high in patients receiving aspirin or clopidogrel with dabigatran compared to those receiving dabigatran alone.⁴⁶ A consistent increase was also observed in those patients receiving aspirin or clopidogrel in addition to warfarin.

Both apixaban and rivaroxaban have been investigated in randomized, prospective trials in the ACS setting in combination with DAPT. In APPRAISE-2 (Phase III Acute Coronary Syndrome), patients were randomized to DAPT plus apixaban 5 mg twice daily or matching placebo;⁴⁷ 97% were taking aspirin, and 81% were treated with DAPT at the time of randomization. An increase in Thrombolysis in Myocardial Infarction group-defined major bleeding was observed with apixaban therapy compared to placebo (HR 2.59, 95% CI 1.50–4.46; $P = 0.001$). The composite of cardiovascular death, MI, or ischemic stroke occurred in 7.5% of patients receiving apixaban and 7.9% of placebo-treated patients (HR 0.95, 95% CI 0.80–1.11; $P = 0.51$). In addition, more fatal (0.1% vs 0.0%) and intracranial (0.3% vs 0.1%, HR 4.06, 95% CI 1.15–14.38; $P = 0.03$) bleeding events occurred in apixaban-treated patients compared to placebo. Although the clinical scenario investigated in APPRAISE-2 may not be necessarily applicable to patients with a separate indication for DAPT and an oral anticoagulant for AF, further analysis from ARISTOTLE may offer additional information regarding this specific issue.

In ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction-51) patients were randomized to receive rivaroxaban 2.5 or 5 mg twice daily or matching placebo in combination with DAPT.⁴⁸ Treatment with rivaroxaban resulted in a significant decrease in the rate of the composite outcome of cardiovascular death, MI, or stroke (8.9% vs 10.7%, HR 0.84, 95% CI 0.74–0.96; $P = 0.008$) compared to placebo-treated patients. Additionally, the 2.5 mg dose was associated with a reduction in the rate of cardiovascular deaths (2.7% vs 4.1%, HR 0.66, 95% CI 0.51–0.86; $P = 0.002$) and all-cause mortality (2.9% vs 4.5%, HR 0.68, 95% CI 0.53–0.87; $P = 0.002$) relative to placebo. In contrast to the observed efficacy benefit, an increase in Thrombolysis In Myocardial Infarction group-defined major bleeding not related to coronary artery-bypass grafting (2.1% vs 0.6%, HR 3.96, 95% CI 2.46–6.38; $P < 0.001$) and a dose-dependent increase in the risk of fatal bleeding (0.1% with 2.5 mg twice daily vs 0.4% with 5 mg twice daily, $P = 0.04$) were observed in patients receiving rivaroxaban.

Recently the 2.5 mg dose of rivaroxaban received regulatory approval from the EMA for use in combination with DAPT in the post-ACS setting.⁴⁹ However it should be noted that the dose studied in ATLAS ACS 2 TIMI 51 (and that approved for use by the EMA) was drastically lower than that evaluated in ROCKET AF in the setting of AF.

Consequently, it is difficult to extrapolate the results of ATLAS ACS 2 TIMI 51 to the broader AF population. In ROCKET AF, treatment with aspirin in addition to rivaroxaban increased the 100-patient-year event rate for major bleeding from 3.02 to 5.82 relative to those receiving rivaroxaban monotherapy.⁵⁰ Among patients receiving DAPT and rivaroxaban or warfarin, the rates of all bleeding subcategories were elevated compared to those receiving only the respective oral anticoagulant. However, no difference in the rate of major bleeding was observed in DAPT-treated patients between the rivaroxaban and warfarin groups.

To date, no data exist detailing concomitant use of any novel oral anticoagulant in combination with newer-generation antiplatelet agents, such as ticagrelor or prasugrel. However, given the data with clopidogrel and novel oral anticoagulants, one might reasonably expect an amplified bleeding risk when these agents are used in combination.

Conclusion

The results of recent clinical trials, such as RE-LY, ARISTOLE, AVERROES, and ROCKET AF, have identified the clinical potential for agents with either enhanced safety or efficacy relative to VKAs. Agents such as dabigatran, apixaban, and rivaroxaban that possess similar or enhanced efficacy for the prevention of thrombotic complications, as well as possessing attractive pharmacologic properties, represent a significant advancement in the overall pharmacologic management of nonvalvular AF. The presence of multiple agents with unique pharmacological and clinically tested properties affords clinicians the opportunity to tailor therapy to the individual patient. Here, we have highlighted the results of the late-stage clinical trials with these agents, as well as multiple patient-specific instances that may lend favorability to one agent over another. In addition to dabigatran, apixaban, and rivaroxaban, the results of phase III trials are pending for edoxaban. Without comparative clinical trials of these novel agents, prescribers are limited to assessments of the individual clinical trials to make therapeutic choices. A broad understanding of both the pharmacologic properties as well as the details of the specific clinical trials is therefore necessary to make informed treatment decisions regarding these agents.

Disclosure

The author reports no conflicts of interest in this work.

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