

The Nonvitamin K Antagonist Oral Anticoagulants And Atrial Fibrillation: Challenges And Considerations

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Abstract

The nonvitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban are used for the reduction of the risk of stroke or systemic embolism (SEE) in patients with nonvalvular atrial fibrillation (NVAF). The purpose of this review is to highlight the safety and efficacy results of the pivotal NOAC clinical trials for use in NVAF, discuss some of the unique management challenges in the use of NOACs in special populations, summarize data on emerging and novel indications, and address potential future directions. A literature search was conducted and to identify relevant clinical trials and studies regarding the use of NOACs for the prevention of stroke or SEE in patients with atrial fibrillation. Relative to warfarin, NOACs are as effective or superior in the prevention of stroke or SEE, and are associated with similar or lower rates of major bleeding and significantly decreased rates of intracranial bleeding, but may be associated with a slightly increased risk of gastrointestinal bleeding in patients with AF. The NOACs are not indicated for use and have not been widely tested in atrial fibrillation patients with other cardiovascular conditions. Additional ongoing and planned clinical trials will provide additional information regarding the use of NOACs in these patients. In situations requiring rapid reversal of anticoagulation, the availability of specific antidotes will improve safety and facilitate NOAC use. Use of NOACs in clinical practice requires consideration of patient characteristics as well as potentially required procedures.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 12% of patients between ages 75 to 84.^[1] It is associated with a 5-fold increased risk of stroke, a 3-fold increased risk of heart failure, and a 2-fold increase in risk of mortality, contributing to >99,000 deaths per year.^[1] Anticoagulation with vitamin K antagonists (VKAs), specifically warfarin, was the standard of care for prevention of stroke and systemic embolic events (SEE) in patients with AF for more than 60 years. However, numerous limitations of warfarin, such as a need for constant monitoring of therapeutic level, food-drug and drug-drug interactions, and person-to-person metabolic variability, have posed challenges in maintenance of appropriate anticoagulant effects, leading to the development of nonvitamin K antagonist oral anticoagulants (NOACs).

Four NOACs are approved by the US Food and Drug Administration (FDA) for stroke prevention in nonvalvular atrial fibrillation (NVAF).^{[2]-[5]} The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend anticoagulation with an oral

anticoagulant based on risk using the CHA₂DS₂-VASc score, with a single point counted for congestive heart failure (C), hypertension (H), diabetes (D), the presence of vascular disease (V), age 65 to 74 (A), and female sex ("sex category" Sc); and 2 points counted for (A) age >75 and (S) prior stroke/thromboembolism.^[1] The AHA/ACC/HRS guidelines recommend either oral anticoagulation with warfarin to an international normalized ratio (INR) 2 to 3 or use of the NOACs approved at the time of writing: dabigatran, rivaroxaban, or apixaban.^[1] Edoxaban was approved by the FDA for stroke prevention in patients with NVAF the following year.^[5]

Despite these treatment guideline recommendations, oral anticoagulation may still be underprescribed and adherence in eligible patients with AF is poor,^{[6]-[8]} presenting a potential barrier to effective stroke prevention in AF. Patients with AF who maintain subtherapeutic INRs have twice the risk of stroke relative to those with INRs from 2 to 3.^[9] Overall, adherence to therapy is the most important factor in decreasing patient risk of stroke or SEE.

This review highlights the safety and efficacy results of pivotal trials for NOACs in patients with NVAF, discusses some of the unique management challenges in the use of NOACs in special populations, summarizes data on emerging and novel indications, and addresses potential future directions.

Pivotal Trial Results

Four large, pivotal phase 3 trials led to the approval of NOACs for stroke and SEE prevention in patients with NVAF (Figure 1).^{[10]-[13]} In these trials, NOACs were associated with similar or lower rates of major bleeding and significantly decreased rates of intracranial hemorrhage (ICH) compared with warfarin by approximately 50%

Key Words

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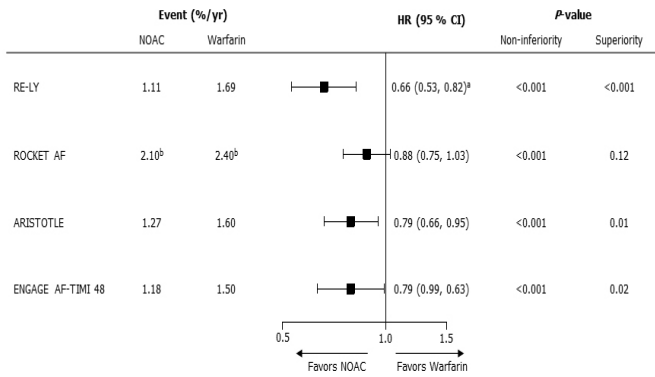


Figure 1:

Forest plot of the hazard ratios (95% CI) for the risk of stroke or systemic embolism with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily compared with warfarin is based on the results of the pivotal clinical trials. ^aData presents as relative risk. ^bReports as number/100 patient-years. ^c97.5% CI. ^dDoes not meet primary superiority endpoint. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; NOAC, nonvitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

(Figure 2).^{[10]-[13]}

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran 150 mg was superior to warfarin in preventing stroke and SEE, and did not differ significantly from warfarin in rates of major bleeding.^[10] Similarly, based on the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was noninferior to warfarin in prevention of stroke and SEE, and did not significantly differ from warfarin in rates of major bleeding.^[11] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was superior to warfarin in prevention of stroke and SEE prevention and had lower rates of major bleeding relative to warfarin.^[12] Lastly, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, higher-dose regimen edoxaban (60/30 mg) was noninferior to warfarin with regards to stroke and SEE prevention and bleeding with dose-dependent lower rates of life-threatening and major bleeding.^[13]

Overall, the above trials showed that, relative to warfarin, NOACs were noninferior or superior in preventing stroke/SEE in patients with NVAf. Rates of ICH were decreased with NOACs relative to warfarin.^{[10]-[13]} Furthermore, while there was a trend towards increased gastrointestinal (GI) bleeding rates for dabigatran,^[10] rivaroxaban,^[11] and edoxaban^[13] were increased relative to warfarin, GI bleeding rates were lower in patients taking apixaban relative to warfarin (Figure 2).^[12]

However, it should be noted that exclusions for GI bleeding differed between trials; patients with symptomatic or endoscopically documented gastroduodenal ulcer in the previous 30 days were excluded from RE-LY, patients with GI bleeds within 6 months of randomization were excluded from ROCKET AF, exclusions for GI bleeding were not defined for ARISTOTLE, and patients with GI bleeds within the past year were excluded from ENGAGE AF-TIMI 48.^{[10]-[13]}

Renal Function

Factors influencing NOAC dosing include renal function, age, body weight, and drug interactions (Table 1). Renal impairment may increase bleeding in patients with NVAf. Overall, the rates of renal excretion between NOACs vary considerably (ie, renal clearance for an absorbed dose of dabigatran is 80%, edoxaban is approximately 50%, rivaroxaban is 36%, and apixaban is 27%).^{[2]-[5]} Assessment of

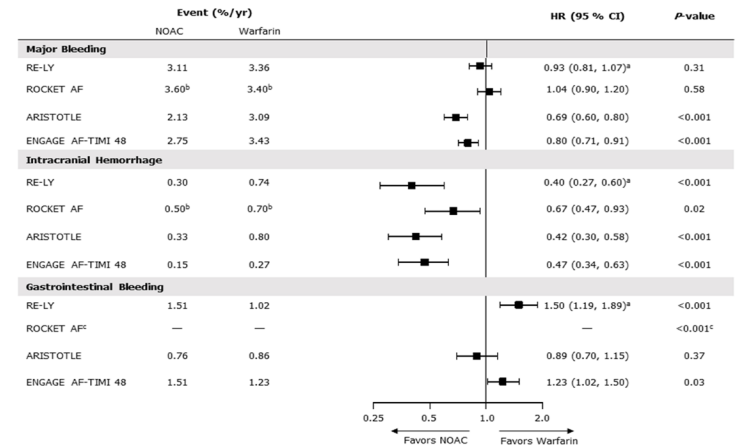


Figure 2:

Forest plot of the hazard ratios (95% CI) for the risk of major or CRNM bleeding, ICH, and GI bleeding with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg compared with warfarin is based on the results of the pivotal clinical trials. ^aData presents as relative risk. ^bReports as number/100 patient-years. ^cMajor bleeding from a GI site occurs in 3.2% of the rivaroxaban group vs 2.2% of the warfarin group. CI, confidence interval; CRNM, clinically relevant nonmajor; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; GI, gastrointestinal; ICH, intracranial hemorrhage; NOAC, nonvitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

renal function prior to beginning treatment regimens with NOACs, and periodically thereafter, is recommended.^{[1]-[3]} It should be noted that patients with end-stage renal disease (ESRD) (creatinine clearance [CrCl] <15 mL/min), were excluded from all the pivotal efficacy trials.^{[2]-[5]} The appropriate NOAC dosing in patients with ESRD on dialysis is not fully elucidated.

For dabigatran, exposure is 1.5 to 3.2 times higher in patients with mild to moderate renal impairment (CrCl of 30–<80 mL/min) compared with patients with a normal CrCl (≥80 mL/min).^[2] Dabigatran should be adjusted to a dose of 75 mg twice daily for patients with severe renal impairment (CrCl of 15–30 mL/min) and for patients with moderate renal impairment (CrCl of 30–50 mL/min) who are also taking dronedarone or systemic ketoconazoles.^[2] The recommendation of a 75-mg, twice-daily dose for patients with renal impairment is based on pharmacokinetic modeling analyses in subjects with renal impairment;^[2] in an open-label, single-center study, mean steady-state drug exposure was similar to predicted exposure.^[14]

Patients with NVAf and a CrCl >50 mL/min should receive rivaroxaban 20 mg once daily with the evening meal; for patients with CrCl of 15 to 50 mL/min, rivaroxaban should be administered as a once-daily 15-mg dose with the evening meal.^[3] In a subanalysis of patients with moderate renal impairment (CrCl of 30–49 mL/min) from the ROCKET AF trial, there were no significant differences in stroke or SEE, major bleeding, or ICH between rivaroxaban 15 mg and warfarin.^[15] However, in a further analysis of the ROCKET AF trial, rivaroxaban was associated with lower rates of stroke or SEE vs warfarin with a similar risk of bleeding in patients with worsening renal function (≥20% decrease from screening CrCl).^[16] Emerging

Table 1: NOAC dosing for NVAF patients general and special populations

Standard Approved Doses	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg once daily with evening meal	Apixaban 5 mg twice daily	Edoxaban ^a 60 mg once daily
Dose adjustments				
Renal function	Reduce dose to 75 mg BID if CrCl 15–30 mL/min. Avoid use for CrCl <30 mL and concomitant P-gp inhibitor. No recommendations if CrCl ≤15 mL/min or on dialysis	No dose adjustment for CrCl >50 mL/min. Reduce dose to 15 mg once daily with the evening meal for CrCl 15–50 mL/min. Avoid if CrCl <30 mL/min	Serum creatinine ≥1.5 mg/dL and body weight ≤60 kg or age ≥80 years: reduce dose to 2.5 mg BID	Reduce dose to 30 mg once daily if CrCl is 15–50 mL/min. CrCl <15 mL/min: not recommended. CrCl >95: not indicated
Elderly	No dose adjustment	No dose adjustment	Age ≥80 years and body weight ≤60 kg or serum creatinine ≥1.5 mg/dL: reduce dose to 2.5 mg BID	No dose adjustment
Low body weight	No dose adjustment	No dose adjustment	Body weight ≤60 kg and age ≥80 years or serum creatinine ≥1.5 mg/dL: reduce dose to 2.5 mg BID	No dose adjustment
Hepatic impairment	Moderate hepatic impairment (Child-Pugh B): no dosing adjustment	Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, or any hepatic disease associated with coagulopathy	No dose reduction for mild hepatic impairment (Child-Pugh A). Moderate hepatic impairment (Child-Pugh B): no dosing recommendations provided. Severe hepatic impairment (Child-Pugh C): not recommended	Mild hepatic impairment (Child-Pugh A): no dose reduction required. Moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment: not recommended
Dual P-gp/CYP3A4 inhibitors	Reduce 75 mg BID dose for patients with moderate renal impairment (CrCl 30–50 mL/min) with ketoconazole, dronedarone. No dose adjustment required for clarithromycin, amiodarone, quinidine, verapamil, ticagrelor	Avoid use with P-gp and strong CYP3A4 inhibitors ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, conivaptan	A 50% dose reduction is recommended for patients receiving a dose >2.5 mg BID when coadministered with strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, itraconazole, ritonavir, or clarithromycin); avoid use of these drugs when dosage is 2.5 mg, BID	No dose adjustment
Dual P-gp/CYP3A4 inducers	Avoid coadministration with rifampin	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid concomitant use of rifampin

^aDo not use edoxaban in patients with CrCl >95 mL/min in the US.

BID, twice daily; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; NOAC, nonvitamin K antagonist oral anticoagulant; NVAF, nonvalvular atrial fibrillation; P-gp, p-glycoprotein.

data may support the efficacy and safety of a 10 mg rivaroxaban dose in ESRD patients;^[17] however, within a population of patients receiving dialysis, rates of hemorrhagic death were greater relative to warfarin for both rivaroxaban 20 mg (rate ratio 1.71; 95% confidence interval [CI] 0.94–3.12) and dabigatran (rate ratio 1.78; 95% CI 1.18–2.68).^[18]

Apixaban dosing recommendations are based on pharmacokinetic and pharmacodynamics data in patients with ESRD maintained on dialysis.^{[19], [20]} Patients with ESRD maintained on intermittent dialysis should receive apixaban at the usually prescribed dose.^[4] In the US, a reduced dose of apixaban (2.5 mg twice daily) is recommended for patients meeting 2 of the following criteria: serum creatinine level ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg.^[4]

In the US, edoxaban is not approved for use in patients with a CrCl >95 mL/min.^[5] For patients with a CrCl of 15 to 50 mL/min, edoxaban should be prescribed at a reduced dose of 30 mg.^[5] In a prespecified subgroup analysis (CrCl 30–50 mL/min vs >50 mL/min) of the ENGAGE AF-TIMI 48 trial, the efficacy, safety, and net clinical benefit of higher-dose edoxaban (60/30 mg) did not differ from warfarin by renal function.^[21] In patients with CrCl >95 mL/min, exploratory analyses identified a statistically insignificant trend toward lower relative efficacy for the prevention of thromboembolic events with edoxaban vs warfarin.^[21] Based on these data, additional studies to determine the optimal dosing of NOACs for patients at the higher range of creatinine clearance and for patients on hemodialysis may be warranted.

Age and Body Weight

Although oral anticoagulants reduce the risk of ischemic stroke in patients with NVAF, there is an increased risk of bleeding, particularly

in the elderly, associated with their use. However, dose reductions for age or body weight are only recommended for patients receiving apixaban who meet 2 of the following criteria: >80 years, body weight <60 kg, serum creatinine ≥1.5 mg/dL.

In a subgroup analysis of ENGAGE AF-TIMI 48, thromboembolic and bleeding risk both increased with age, with more pronounced risk—especially for major bleeding—in patients with age ≥75 years.^[22] However, regardless of age, edoxaban was associated with a similar reduction in the risk of stroke or SEE and a lower risk of major bleeding vs warfarin^[22]. Therefore, due to the higher bleeding risk in the elderly relative to younger patients, the primary net clinical benefit (stroke/SEE/major bleeding/death) of edoxaban vs warfarin was improved in older patients.^[22] Similarly, in a subgroup analysis of the AVERROES (Apixaban Versus ASA to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, apixaban was more effective than aspirin for preventing strokes or SEE in patients ≥85 years with no significant treatment-by-age interaction for bleeding.^[23]

Drug Interactions

All NOACs are substrates of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) metabolizes all NOACs, except dabigatran, to some degree.^[2–5] Inducers of P-gp or CYP3A4 may lead to a decrease in NOAC exposure and effectiveness while inhibitors of P-gp or CYP3A4 may increase NOAC exposure and increase the risk of bleeding.^[2–5] All NOACs are contraindicated for coadministration with rifampin, a potent P-gp/CYP3A4 inducer, while guidance on coadministration with various P-gp or CYP3A4 inhibitors varies between the NOACs.^[2–5]

Table 2: Select ongoing clinical trials

Study	Trial Name	NOAC Treatment Arm	Phase	ClinicalTrials.gov Identifier
Cardioversion/ablation	—	Dabigatran	4	NCT01976507
	ABRIDGE-J ^[58]	Dabigatran	4	—
	RE-CIRCUIT ^[59]	Dabigatran	4	NCT02348723
	—	Dabigatran	3	NCT02313584
	OCEAN	Rivaroxaban	4	NCT02168829
	EMANATE	Apixaban	4	NCT02100228
	AXAFA	Apixaban	4	NCT02227550
PCI	ENSURE-AF ^[60]	Edoxaban	3	NCT02072434
	OAC-ALONE	Any NOAC	4	NCT01962545
	REDUAL-PCI	Dabigatran	3	NCT02164864
	PIONEER	Rivaroxaban	3	NCT01830543
	AF-PCI ^[65]	—	—	—
CAD/PAD	—	Rivaroxaban	4	NCT02334254
	SAFE-A	Apixaban	4	—
	—	Dabigatran	4	NCT02389582
	AFIRE	Rivaroxaban	4	NCT02642419
	COMPASS	Rivaroxaban	3	NCT01776424
Nondisabling cerebrovascular events (TIA/minor stroke)	VOYAGER PAD	Rivaroxaban	3	NCT02334254
	EDOX-APT	Edoxaban	4	NCT02567461
	TRACE ^[67]	Rivaroxaban	2 and 3	NCT01923818
Device-detected subclinical AF	ADANCE ^[66]	Apixaban	2 and 3	NCT01924325
	—	Edoxaban	2 and 3	NCT02221102
TAVR	ARTESIA	Apixaban	4	NCT01938248
	NOAH	Edoxaban	3	NCT02618577
Type 2 diabetes	GALILEO	Rivaroxaban	3	NCT02556203
	ATLANTIS	Apixaban	3	NCT02664649
MicroVasc-DIVA	Rivaroxaban	3	NCT02164578	

ABRIDGE-J, Ablation Perioperative Dabigatran in Use Envisioning in Japan; ADANCE, Apixaban vs Therapy (Clopidogrel and Aspirin) in Acute Nondisabling Cardiovascular Events; AF, atrial fibrillation; AFIRE, Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; ATLANTIS, Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; ARTESIA, Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; AXAFA, Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy; CAD, coronary artery disease; COMPASS, Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; EDOX-APT, Edoxaban in Patients with Coronary Artery Disease on Dual Antiplatelet Therapy with Aspirin and Clopidogrel; EMANATE, Eliquis Evaluated in Acute Cardioversion Compared to Usual Treatment for Anticoagulation in Subjects with NVAF; ENSURE-AF, Edoxaban vs Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation; GALILEO, Global Study Comparing Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes; MicroVasc-DIVA, Microvascular and Anti-inflammatory Effects of Rivaroxaban Compared to Aspirin in Type-2 Diabetic Patients with Cardiovascular Disease; NOAH, Nonvitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes; OAC-ALONE, Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stent; OCEAN, Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RE-CIRCUIT, Uninterrupted Dabigatran Etxilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation; REDUAL-PCI, Triple Therapy with Warfarin in Patients with AF that Undergo a PCI with Stenting; SAFE-A, Safety and Effectiveness Trial of Apixaban Use in Association with Dual Antiplatelet Therapy in Patients with Atrial Fibrillation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; TRACE, Treatment of Rivaroxaban vs Aspirin for Non-disabling Cardiovascular Events; VOYAGER PAD, Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects with Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities.

Coadministration of rivaroxaban and apixaban with the strong P-gp/CYP3A4 dual inducers such as carbamazepine, phenytoin, and St. John's wort should be avoided.^[3, 4] Strong P-gp/CYP3A4 inhibitors such as ketoconazole and ritonavir should be avoided in patients taking rivaroxaban, and patients taking dabigatran and apixaban may require a dose reduction with concomitant use of strong P-gp/CYP3A4 inhibitors.^[2-5] For concomitant use of NOACs with less potent P-gp/CYP3A4 inhibitors (eg, amiodarone, diltiazem, and verapamil), no dose adjustment is recommended.^[2-5] As edoxaban is not significantly metabolized by CYP3A4, there is no recommendation for a dose reduction of edoxaban with dual P-gp/CYP3A4 inhibitors when used for the prevention of stroke/SEE in patients with NVAF^[5]. Patients undergoing concomitant

treatment with NOACs and other anticoagulants, nonsteroidal anti-inflammatory drugs, aspirin, or antiplatelet medications should be closely monitored for symptoms of bleeding or blood loss due to an increased bleeding risk.^[2-5] In a study in which patients received single antiplatelet treatment, primarily aspirin, in combination with edoxaban, patients receiving edoxaban and antiplatelet therapy had higher rates of major bleeding (hazard ratio [HR] 1.46; 95% CI 1.27–1.67; P<0.001) relative to those receiving edoxaban alone, with no difference in rates of stroke or SEE (HR 1.12; 95% CI 0.95–1.32).^[24]

Emerging and Novel Indications Valvular Heart Disease

Although NOACs are not approved for patients with AF and valvular heart disease, several clinical trials and subgroup analyses of phase 3 trials have been performed to assess the efficacy and safety of NOACs in AF patients with valvular disease. Patients with mild mitral stenosis were not excluded from either the edoxaban or apixaban phase 3 clinical trials.^{[12], [13]} In a subgroup analysis of ARISTOTLE, there were no differences between apixaban and warfarin in preventing stroke or SEE, reducing death, or causing bleeding in patients with or without valvular heart disease.^[25]

Dabigatran is the only NOAC investigated in clinical trials in patients with mechanical heart valves. The phase 2 dose-validation study RE-ALIGN (Randomized Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients after Heart Valve Replacement) was terminated early due to excess thromboembolic and bleeding events in patients randomized to dabigatran.^[26] In RE-ALIGN, 5% of patients on dabigatran and no patients on warfarin experienced a stroke.^[26] Major bleeding occurred in 4% of dabigatran patients and 2% of warfarin patients; bleeding of any type occurred in 27% of dabigatran patients and 12% of warfarin patients.^[26]

Few clinical studies have assessed the efficacy and safety of patients with AF and bioprosthetic valves. However, in a small, retrospective, single-center cohort study of AF patients with bioprosthetic valves who were prescribed NOACs, approximately 100 days after bioprosthetic valve implantation 8.2% (6/73) of patients reported a minor bleeding event and 6.9% (5/73) reported a major bleeding event with no ischemic strokes.^[27]

Peripheral Arterial Disease

In a subgroup analysis of the ENGAGE AF-TIMI 48 trial, regardless of the presence or absence of peripheral arterial disease (PAD), higher-dose edoxaban (60/30 mg once daily) had similar efficacy and safety relative to warfarin.^[28] Similarly, in a subgroup analysis of the ROCKET AF trial, rivaroxaban had a similar efficacy compared with warfarin in patients with and without PAD.^[28] However, patients with PAD had a higher risk of bleeding with rivaroxaban vs warfarin compared with patients without PAD (P=0.037).^[28]

Diabetes is a risk factor for PAD and PAD-associated mortality; individuals with comorbid diabetes and PAD are at approximately twice the risk of death compared with patients with PAD alone.^[29] Consistent with this, in a subgroup analysis of the RE-LY study, the incidence of peripheral vascular disease was higher in diabetic patients as compared with non-diabetic patients.^[30] In addition, the numerical reduction in stroke or SEE associated with dabigatran relative to warfarin was greater in diabetic patients compared with

nondiabetic patients (dabigatran 150 mg twice daily: 0.89% per year vs 0.51% per year).^[30]

The COMPASS trial (clinicaltrials.gov NCT01776424)—which recruited more than 27,000 patients and examined the efficacy of low-dose rivaroxaban against aspirin in patients with documented coronary artery disease or PAD—was recently stopped early for “overwhelming efficacy”.^[31] Full study results will be available later this year.

Myocardial Infarction

Following reanalysis of the by request of the FDA, rates of myocardial infarction (MI) did not differ significantly between dabigatran and warfarin^{[10], [32], [33]}, although initial analyses showed increased risk of MI was associated with dabigatran use. Some studies suggest dabigatran may be associated with an increased risk for MI, but the data are mixed.^{[10], [32]-[35]} In the initial analysis of the RE-LY trial, dabigatran 150 mg twice daily was associated with increased rates of MI vs warfarin (0.74% vs 0.53% per year, respectively; relative risk = 1.38; [95% CI 1.00–1.91]; P=0.048).^[10] Following re-evaluation of the database for possible event underreporting, these rates were subsequently revised to 0.81% vs 0.64% per year, respectively (relative risk = 1.27; 95% CI 0.94–1.71; P=0.12).^[32] It should be noted that in RE-LY, patients who had ≥ 1 MI were older and had more coronary risk factors compared with those who did not experience an MI event.^[33] In the ENGAGE AF-TIMI 48 and the ROCKET AF trials, there were no differences in safety between edoxaban and warfarin or between rivaroxaban and warfarin in patients with prior MI.^{[11], [13]} There have been no subgroup analyses for apixaban and MI.

Cardioversion

Overall, the incidence of stroke in patients with NVAF who undergo cardioversion tends to be greater within the first 30 days postprocedure relative to the period ranging from 30 days to 3 years.^[36] Data for the use of NOACs following cardioversion are limited; however, several post hoc analyses of the phase 3 NVAF trials and 2 phase 3b trials were conducted.

In RE-LY, rates of stroke and major bleeding associated with dabigatran vs warfarin within 30 days of cardioversion were comparable.^[37] Similarly, in an analysis of ROCKET AF, the long-term stroke rates, rates of survival following cardioversion, or ablation associated with rivaroxaban did not differ compared with warfarin.^[38] In ARISTOTLE, major cardiovascular events following cardioversion were similar between patients receiving apixaban and warfarin.^[39] Thromboembolic and major bleeding events within 30 days of cardioversion were infrequent and similar between edoxaban and warfarin treatments in the ENGAGE AF-TIMI 48 trial.^[40] Consistent with these results, in a meta-analysis of 4 randomized controlled trials for NOACs, NOACs were at least as effective and safe as VKA for NVAF patients undergoing cardioversion procedures.^[41]

The first randomized trial of a NOAC in patients with NVAF undergoing elective cardioversion was X-VerT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTtrial fibrillation scheduled for cardioversion).^[42] In X-VerT, patients were randomized to receive rivaroxaban (20 mg/15 mg for CrCl 30–49 mL/min) or VKA therapy for 1 to 5 days or for 3 to 8 weeks prior to cardioversion, respectively.^[42] In patients with delayed cardioversion, adequate VKA treatment required an INR in the range of 2.0 to 3.0

for at least 3 consecutive weeks prior to cardioversion.^[42] Compared with VKA therapy, rivaroxaban was associated with similar rates of stroke or other cardiovascular events and bleeding, but a significantly shorter time to cardioversion.^[42]

A second trial, edoxaban vs enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF), enrolled 2,199 patients to receive edoxaban (60 mg/30 mg for CrCl 15–50 mL/min, body weight ≤ 60 kg or concomitant use of P-gp inhibitors) or enoxaparin/warfarin.^[43] Rates of major bleeding and thromboembolism were similar between patients treated with edoxaban and those treated with enoxaparin-warfarin, regardless of the use of conventional or transesophageal echocardiography, previous use of anticoagulation, edoxaban dose, or region.^[43] In the overall population, the composite endpoint of stroke, SEE, MI, cardiovascular mortality, and major bleeding occurred in 5 patients treated with edoxaban and 11 patients treated with enoxaparin-warfarin (odds ratio 0.46, 95% CI 0.12–1.43).^[43] The difference between treatment groups was primarily driven by lower cardiovascular mortality in the edoxaban group (0.1%) vs the enoxaparin-warfarin group (0.5%).^[43]

Similarly, in a cohort study comparing the efficacy and safety of dabigatran vs warfarin in NVAF patients undergoing cardioversion, dabigatran was associated with a similar risk of adverse events and NVAF readmission vs warfarin, but a shorter time to cardioversion.^[44] In a real-world clinical setting, rates of cerebrovascular accidents or transient ischemic attacks (warfarin: 0.97% vs NOAC 1.62%, P=0.162) and bleeding events (warfarin: 1.02% vs NOAC: 0.5%, P=0.247) were low in patients with NVAF undergoing direct current cardioversion who were prescribed periprocedural anticoagulants.^[45] Together, these studies indicate that NOACs may be a safe and effective alternative to warfarin in patients undergoing elective electrical cardioversion.

Chronic Obstructive Pulmonary Disease

Comorbid chronic obstructive pulmonary disease (COPD) is associated with poor outcomes among patients with cardiovascular disease.^[46] However, the efficacy and safety of NOACs among patients with NVAF and COPD is not well studied. In a subanalysis of the ARISTOTLE trial, comorbid COPD was associated with an elevated risk of all-cause mortality (adjusted HR 1.60; 95% CI 1.36–1.88; P<0.001).^[47] In this same analysis, the reported benefits of apixaban vs warfarin in reducing the risk of stroke or SEE, bleeding, and all-cause mortality were independent of COPD status.^[47]

Patients Undergoing Interventional Procedures

Patients with NVAF who require surgery or interventional procedures associated with bleeding risk may require interruption of anticoagulation. There is little specific research to guide physicians in the determination of whether procedures should be performed in the presence of anticoagulation or following temporary discontinuation of treatment. The AHA/ACC/HRS guidelines note that the NOACs provide a more prompt return to anticoagulation, although limited availability of reversal agents may complicate management of bleeding.^[1] Risk of bleeding should be weighed against the urgency of intervention.

Dabigatran should be discontinued 1 to 2 days prior to procedures in patients with a CrCl ≥ 50 mL/min, or 3 to 5 days prior in patients with a CrCl <50 mL/min.^[2] For urgent surgery or procedures, a specific reversal agent is available.^[2, 48] Treatment with rivaroxaban or edoxaban should be discontinued at least 24 hours prior to a procedure.

[3, 5] Use of a parenteral anticoagulant should be considered in the event that oral medication cannot be taken during or after surgical intervention.^[3, 5] Apixaban should be discontinued 48 hours prior to elective surgery or invasive procedures associated with a moderate or high risk of unacceptable or clinically significant bleeding; discontinue use of apixaban 24 hours prior to low-risk procedures or those in which bleeding is in a noncritical location and can be easily controlled.^[4] Bridging is not typically required 24 to 48 hours after stopping apixaban and prior to the intervention.^[4] Typically, the NOACs can be reinitiated once hemostasis is established and treatment is medically appropriate.^[2-5]

A few small, single-center studies have examined the use of dabigatran and rivaroxaban in patients undergoing implantation of permanent pacemaker or implantable cardioverter defibrillators.^[49-51] Few complications occurred in these studies, regardless of treatment. Patients receiving anticoagulation at the time of implantation of a permanent pacemaker or implantable cardioverter defibrillator more commonly experienced pocket hematoma, relative to patients not receiving an oral anticoagulant.^[50, 51] Nonsignificant increases in bleeding complications following interrupted rivaroxaban treatment relative to interrupted dabigatran treatment were reported in two studies.^[49, 50] As data are limited, no formal treatment recommendations have been issued regarding the use of NOACs in this procedure.

Likewise, a limited number of studies have assessed NOACs in the setting of catheter ablation, although there are no formal treatment recommendations to date. Periprocedural use of NOACs prior to ablation is associated with low rates of complications, thromboembolic events, or minor bleeding events relative to warfarin.^[52-56] In one multicenter registry, uninterrupted use of rivaroxaban was as safe and effective as warfarin during catheter ablation.^[57] As mentioned above, the COMPASS trial included patients with coronary artery disease and previous revascularization. The role of NOACs, specifically rivaroxaban, in this setting will be clearer once full results are presented.

Reversal Agents

Despite the lower risk of bleeding relative to warfarin associated with NOACs, the lack of reversal agents for NOACs remains a major concern. Reversal agents could be of use in certain situations following the administration of NOACs including life-threatening bleeding, bleeding into a critical organ or closed space, prolonged bleeding, NOAC overdose or delayed clearance, emergency surgery, or urgent interventions associated with high bleeding risks.^[58] Several reversal agents have recently received approval or are in clinical development.

Idarucizumab

Idarucizumab, a human antibody fragment, is the first approved NOAC antidote indicated for the reversal of dabigatran when bleeding cannot be controlled.^[48] Idarucizumab binds free and thrombin-bound dabigatran with high affinity, thereby neutralizing its activity.^[59] In a phase 3 clinical trial, idarucizumab nearly fully neutralized the anticoagulant effect of dabigatran in patients who experienced serious bleeding or required an urgent procedure.^[59] Several other reversal agents are in development for NOACs.

Andexanet Alfa

In phase 2 and 3 clinical trials, andexanet alfa (PRT064445, Portola Pharmaceuticals, Inc., South San Francisco, CA), a recombinant

catalytically inactive FXa decoy molecule, rapidly reversed the effect of rivaroxaban and apixaban.^{[58], [60]} Similar results were reported for edoxaban reversal in a phase 2 clinical trial.^[61] Andexanet alfa is currently under regulatory review as a universal antidote for factor Xa inhibitors.^[62]

Ciraparantag

Ciraparantag (PER977, Perosphere, Inc., Danbury, CT), a synthetic small molecule that binds all 4 NOACs via hydrogen bonds, is in early-phase trials for the reversal of NOACs. In a phase 1 study in healthy volunteers receiving edoxaban, ciraparantag dose-dependently shortened whole blood clotting time and restored normal clot architecture.^[58]

Prothrombin Concentrate Complexes

Prothrombin concentrate complexes (PCCs), pooled plasma products containing concentrations of 3 factors (II, IX, and X) or 4 factors (II, VII, IX, and X) and vitamin K-dependent proteins, are under clinical investigation for the reversal of NOAC anticoagulation. The studies with PCCs have had variable results; if administration is necessary, careful consideration must be given to the increased risk of thromboembolism associated with administration of these products.^{[63], [64]}

Future Directions

Table 2 shows a partial listing of planned or ongoing clinical trials assessing the efficacy and safety of NOACs for emerging indications including percutaneous coronary intervention (PCI), and nondisabling stroke. These additional clinical trials will hopefully provide further information regarding the use of NOACs in these and other indications.

Percutaneous Coronary Intervention

NOACs are not indicated for antithrombotic management of patients with NVAF undergoing PCI with stenting. However, there are several ongoing clinical trials assessing the use of NOACs in these patients. The PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; clinicaltrials.gov NCT01830543) is an exploratory, open-label, randomized trial assessing the safety of 2 rivaroxaban dual-antiplatelet treatment regimens compared with a triple-antiplatelet treatment regimen including VKA in NVAF patients with ischemic heart disease who have undergone PCI with stent placement (bare metal or drug-eluting stent).^[65] The primary endpoint is a composite of the rate of major bleeding, bleeding requiring medical attention, and minor bleeding at 12 months.^[65] Similarly, REDUAL-PCI (Randomized Evaluation of Dual Therapy with Dabigatran vs Triple Therapy Strategy with Warfarin in Patients with NVAF that have undergone PCI with Stenting; clinicaltrials.gov NCT02164864) is assessing the safety of 2 dabigatran dual-antiplatelet treatment regimens compared with a triple antiplatelet treatment regimen including VKA in patients with NVAF and ischemic heart disease who have undergone stent placement (bare metal or drug-eluting stents). The primary outcome is the time to first major or clinically relevant nonmajor bleeding event.

Non-Disabling Stroke

No clinical trials assessing the efficacy and safety of NOACs for preventing transient ischemic attack (TIA) and acute minor ischemic stroke have completed; 3 randomized trials are ongoing. ADANCE

(Apixaban Versus Dual-antiplatelet Therapy [Clopidogrel and Aspirin] in Acute Non-disabling Cerebrovascular Events; clinicaltrials.gov NCT01924325) is a randomized, double-blind clinical trial comparing a regimen of apixaban or clopidogrel with aspirin followed by clopidogrel in patients with acute TIA or minor ischemic stroke.^[66] Similarly, TRACE (The Treatment of Rivaroxaban versus Aspirin in Nondisabling Cerebrovascular Events; clinicaltrials.gov NCT01923818) is a randomized, double-blind clinical trial comparing rivaroxaban with aspirin in patients with acute TIA or minor stroke.^[67] There is one planned randomized, double-blind clinical trial (clinicaltrials.gov NCT02221102) comparing edoxaban with aspirin alone in patients with acute TIA or minor stroke. In all 3 planned clinical trials, the primary efficacy endpoint is the percentage of patients with new stroke (ischemic or hemorrhage).

Conclusions

In patients with NVAF, NOACs are at least noninferior to warfarin in preventing stroke or SEE and are associated with a decreased risk of ICH compared with warfarin. These agents may, however, be associated with a slightly increased risk of GI bleeding relative to warfarin. In general, NOACs may offer a significant advantage over warfarin for most patients, and unlike warfarin, do not require frequent laboratory monitoring. It is important to note that the available NOACs vary in dosing regimens and require dose adjustments in patients with compromised renal function based on specific criteria for each individual agent. Therefore, when considering the appropriate dose and adequate use of these agents, several important factors should be considered, especially in patients with renal impairment or cardiovascular conditions other than NVAF. Overall, the appropriate use of NOACs requires following guidelines and prescribing instructions.

NOACs are not indicated for use and have not been widely tested in AF patients with other cardiovascular conditions. Subgroup analyses of the phase 3 trial data, small clinical trials, and observational studies provide some insights into this area. Additional ongoing and planned clinical trials will provide additional information regarding the use of NOACs in these patients. In situations requiring rapid reversal of anticoagulation such as life-threatening bleeding, NOAC overdose, and emergency surgery, the availability of specific antidotes will improve safety and facilitate the use of NOACs.

Conflict Of Interests

Dr. Plitt has no disclosures. Dr. Bansilal has received institutional research grant support from AstraZeneca and consulting fees from AstraZeneca and Janssen.

Disclosures

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