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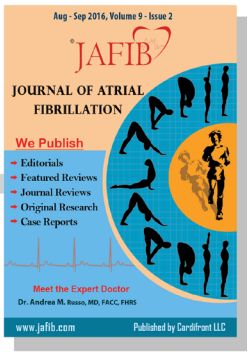

Reducing The Risk Of Stroke In Patients With Nonvalvular Atrial Fibrillation With Direct Oral Anticoagulants. Is One Of These Not Like The Others?

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and increases risk of stroke by nearly 5-fold. While warfarin has been employed successfully to reduce the risk of stroke in these patients, there are a number of challenges with therapy. These include the need for therapeutic monitoring due to variability in patient response, frequent dose adjustments, numerous drug-drug, drug-food, and drug-disease interactions, and a heightened risk of thrombosis and bleeding due to these issues. Current guidelines recommend that the vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs) should be used for thromboprophylaxis in patients with nonvalvular AF at risk for stroke or systemic embolic events. The DOACs include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. In clinical trials these agents consistently demonstrated a reduction in the risks of hemorrhagic stroke and intracranial hemorrhage compared to VKA. Clinicians now must decide if there are meaningful differences between these agents in order to prescribe the best agent for an individual patient. Therefore, it is critical for clinicians to go beyond information provided in manuscript abstracts, and gain an understanding of the similarities and differences in clinical trial design, patient enrollment, and statistical analysis.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with a 4- to 5-fold increased risk of ischemic stroke.[1] The incidence of AF increases with age and presents with a wide spectrum of symptoms and severity. The forms of AF; paroxysmal, persistent, and permanent, all require individualized management, which may range from medical therapy to interventional procedure to device implantation. Atrial fibrillation is estimated to afflict as many as 6 million patients in the Unites States and as many as 34 million patients worldwide. Its prevalence is projected to double over the next 25 years, magnifying the management burden to health care providers.

Although stroke is the most feared complication of AF, stroke rates have declined over the last decade by virtue of patients taking oral anticoagulants.[1] Vitamin K antagonists (VKAs) were the cornerstone of stroke prevention for over 50 years. While VKA administration can effectively reduce the stroke rate by two-thirds, registry and hospital level data suggest they are frequently under prescribed, reaching only about 50% of eligible patients.[2-3] Furthermore, the stroke reduction benefit and bleeding risk are directly associated with the percentage of time the International Normalized Ratio (INR) is within a targeted range. Both registry and clinic level data suggest time in therapeutic range (TTR) is suboptimal and often associated with poor outcomes and higher healthcare costs.[4-7]

In the past several years direct acting oral anticoagulants (DOACs) have emerged as alternatives to VKAs. Collectively, they have been shown to provide better efficacy in stroke reduction and intracranial hemorrhage with at least a similar incidence of major bleeding when compared to VKAs.[8] In addition, they require no laboratory monitoring, can be administered in fixed doses, and improve long term persistence.[9] There are, however, differences in their pharmacokinetic profiles and specifics in the individual trial design that are important for clinicians to consider in their prescribing.[10] This review is intended to highlight the important similarities and differences of these agents as they relate to use in AF.

Phase 3 Clinical Trials

Each of the four currently available DOACs has a phase 3 clinical trials evaluating its efficacy and safety compared to a VKA, mainly warfarin, in patients with nonvalvular atrial fibrillation (NVAF). These studies include the evaluation of dabigatran, rivaroxaban,

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Table 1: Comparison of clinical trial design for DOAC clinical trials in patients with NVAF[11-14]

	RE-LY (dabigatran)	ROCKET AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF-TIMI 48 (edoxaban)
Study Design	Randomized, dabigatran dosage-blinded, open-label warfarin, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy, event-driven, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy trial, parallel-arm, noninferiority study
Primary Endpoint (analysis population)	Stroke or systemic embolism (ITT)	Stroke or systemic embolism (PP)	Stroke or systemic embolism (ITT)	Stroke or systemic embolism (mITT)
Dosage	Dabigatran 110 mg or 150 mg BID, or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Rivaroxaban 20 mg once daily or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Apixaban 5 mg BID or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Edoxaban 30 mg or 60 mg once daily, or warfarin dose-adjusted to a target INR of 2.0 to 3.0
Dose reduction	None	15 mg once daily for patients with a CrCl of 30 to 49 mL/min	2.5 mg BID in a subset of patients with 2 or more of the following criteria: age ≥80, body weight ≤60 kg, or serum creatinine ≥1.5mg/dL	50% dose reduction was given to patients with CrCl 30-50 mL/min, body weight ≤60 kg, or concomitant use of verapamil, quinidine, or dronedarone at randomization or during study

DOAC = direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; ITT = intention to treat population; PP = per protocol as-treated population during treatment; mITT = modified intention to treat; BID = twice daily; INR = international normalized ratio; CrCl = creatinine clearance

apixaban, and edoxaban in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran etexilate) trial,[11] the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial,[12] the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial,[13] and the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48) trial,[14] respectively. All patients included in these trials were at an increased risk of stroke due to one or more additional risk factors, such as previous stroke or transient ischemic attack (TIA), heart failure, diabetes mellitus, hypertension, or age ≥ 75 years. All four trials were noninferiority trials, which are typically designed to evaluate a per-protocol or modified intention to treat (mITT) population (Table 1). Use of intent-to-treat population (ITT) compared to an on-treatment populations for noninferiority study is controversial and the Food and Drug Administration (FDA) recommends that results for noninferiority analyses be reported for both populations.[15,16] The inclusion of all patients randomized to treatment in the ITT population avoids biases associated with switching treatment, dropout patterns, or patient selection. However, these analyses also include patient outcomes that occur after patients have ceased treatment, including patients with poor compliance. There were differences in the reported populations analyzed for the primary efficacy endpoints: RE-LY and ARISTOTLE reported noninferiority for their ITT populations,[11,13] ROCKET AF reported for the per-protocol population,[12] and ENGAGE AF analyzed the mITT population.[14]

Primary efficacy endpoint in all of these trials was the incidence of stroke (ischemic or hemorrhagic) and systemic embolic events (SEE) (Table 1). All studies used an adapted version of the International Society of Thrombosis and Hemostasis (ISTH) criteria for major and clinically relevant nonmajor (CRNM) bleeding.[17] Major bleeding was the primary safety outcome in the RE-LY, ARISTOTLE, and ENGAGE AF trials, while the ROCKET AF trial use the composite of major and CRNM as the primary safety endpoint. The RE-LY, ROCKET AF, and ARISTOTLE trials had a median follow up time of about 2 years, while the ENGAGE AF trial had a median follow up period of 2.8 years.

Dabigatran

The first trial to evaluate the efficacy and safety of a DOAC compared to warfarin for the reduction of risk of stroke and SEE in patients with NVAF was the RE-LY trial.[11] Patients (n=18,113) were randomized to either dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or dose-adjusted warfarin. While dabigatran was administered in a blinded fashion, dose-adjusted warfarin was administered in a non-blinded fashion.

Compared to dose-adjusted warfarin, dabigatran 110 mg twice daily demonstrated noninferiority in prevention of the primary endpoint [relative risk (RR) 0.91, 95% confidence interval (CI) 0.74 – 1.11; p <0.001 for noninferiority), while dabigatran 150 mg twice daily proved to be superior in the prevention of the primary endpoint (RR 0.66, 95% CI 0.53 – 0.82; p <0.001 for superiority) (Table 2).11 While both doses of dabigatran significantly reduced the risk of hemorrhagic stroke compared with warfarin (RR 0.31, 95% CI 0.17 – 0.56; p <0.001 for dabigatran 110 mg; RR 0.24, 95% CI 0.14 – 0.49; p<0.001 for dabigatran 150 mg), ischemic stroke was also significantly reduced with the use of dabigatran 150 mg twice daily compared to warfarin (RR 0.76, 95% CI 0.60 – 0.98; p = 0.03).[11] It should be noted that event rates for dabigatran were updated following publication of the primary data to reflect inclusion of events potentially related to stroke, as well as the addition of patients who did not undergo randomization and several deaths that occurred after the end of the study.[18,19]

The rate of major bleeding was similar in patients randomized to dabigatran 150 mg twice daily compared to adjusted-dose warfarin (RR 0.93, 95% CI 0.81 – 1.07; p = 0.31), and lower in patients who received dabigatran 110 mg twice daily compared to warfarin (RR 0.80, 95% CI 0.69 – 0.93, p = 0.003) (Table 3).[11] There was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150 mg twice daily compared to warfarin (RR 1.50, 95% CI 1.19 – 1.89; p <0.001). The rate of intracranial bleeding was significantly reduced in patients receiving dabigatran 150 mg (RR 0.40, 95% CI 0.27 – 0.60; p <0.001) or dabigatran 110 mg (RR 0.31, 95% CI 0.20 – 0.47; p <0.001) compared with warfarin.[21] The incidence of other adverse events were similar between groups, except the rate of dyspepsia. Dyspepsia was significantly more common in patients receiving dabigatran 110 mg twice daily (11.8%) and 150 mg twice daily (11.3%) compared with warfarin (5.8%; p <0.001 for both comparisons).[11]

While a renally-adjusted dose of dabigatran was not evaluated in the RE-LY trial, pharmacokinetic data support the use of a 75 mg twice daily dose in patients with a creatinine clearance (CrCl) of 15 to 30 mL/min.[20] Efficacy and safety data are not available for this dose of dabigatran.

Rivaroxaban

The ROCKET AF trial was a double-blind, double-dummy trial in which patients with NVAF were randomized to rivaroxaban 20

Table 2: Efficacy of DOACs compared with warfarin in phase 3 trials in patients with NVAF[11-14]

	RE-LY			ROCKET AF		ARISTOTLE		ENGAGE AF – TIMI 48		
	Dabigatran							Edoxaban		
Outcome (%)a,b	110 mg	150 mg	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Low Dose	High Dose	Warfarin
Stroke or SEE (ITT) p-value	1.54 p=0.27	1.11 p<0.001	1.69	2.1 p=0.12	2.4	1.27 p=0.01	1.60	2.04 p=0.10	1.57 p=0.08	1.80
Stroke or SEE (PP or mITT)c p-value	NR	NR	NR	1.7 p=0.015	2.2	NR	NR	1.61 p=0.44	1.18 p=0.02	1.50
Total stroke p-value	1.44 p=0.41	1.01 p<0.001	1.57	1.65 p=0.092	1.96	1.19 p=0.01	1.51	1.91 p=0.12	1.49 p=0.11	1.69
Ischemic stroke p=value	1.34 p=0.35	0.92 p=0.03	1.20	1.34 p=0.581	1.42	0.97 p=0.42	1.05	1.77 p<0.001	1.25 p=0.97	1.25
Hemorrhagic stroke p-value	0.12 p<0.001	0.26 p<0.001	0.38	0.26 p=0.024	0.44	0.24 p<0.001	0.47	0.16 p<0.001	0.26 p<0.001	0.47
SEE p-value	NR	NR	NR	0.04 p=0.003	0.19	0.09 p=0.70	0.10	0.15 p=0.43	0.08 p=0.19	0.12
Total mortality p-value	3.75 p=0.13	3.64 p=0.051	4.13	1.87 p=0.07	2.21	3.52 p=0.047	3.94	3.80 p=0.006	3.99 p=0.08	4.35

DOAC=direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; SEE=systemic embolic event; ITT=intention to treat; PP=per protocol; mITT=modified intention to treat
a All p values for superiority.
b Event rate for RE-LY, ARISTOTLE, and ENGAGE AF are in %/year; for ROCKET AF, number/100 patient years
c ROCKET AF evaluated data in the per protocol safety analysis and ENGAGE AF-TIMI 48 evaluated data in the modified intention to treat analysis

mg daily or dose-adjusted warfarin.[12] Patients with a CrCl of 30 to 49 mL/min and randomized to rivaroxaban received a 15 mg daily dose instead of 20 mg daily.

At the end of follow up, rivaroxaban demonstrated noninferiority to warfarin for the prevention of the primary endpoint (HR 0.79, 95% CI, 0.66 – 0.96; p <0.001 for noninferiority).[12] Rivaroxaban demonstrated superiority in the on-treatment analysis (p = 0.015), but not in the ITT analysis (p = 0.12) (Table 2). The rate of hemorrhagic stroke was significantly reduced in the rivaroxaban group compared with the warfarin group, but with no statistical difference in the rate of ischemic stroke (Table 2).

Major bleeding was similar between patients receiving rivaroxaban and warfarin (HR 1.04, 95% CI 0.90 – 1.20) (Table 3).[12] While patients receiving rivaroxaban experienced significantly less intracranial hemorrhage (ICH) (HR 0.67, 95% CI, 0.47 – 0.93; p = 0.02) and fatal bleeding (HR, 0.50, 95% CI, 0.31 – 0.79; p = 0.003) compared to patients receiving warfarin, there were more major GI bleeding (3.2% vs. 2.2%; p <0.001) and a higher need for transfusion (2.6% vs 2.15%; p=0.04) with the use of rivaroxaban compared to warfarin. Major and CRNM bleeding rates were similar between groups (HR 1.03, 95% CI 0.96 – 1.11). Rates of other adverse events were similar between groups.

The reduced dose of rivaroxaban (15 mg once daily) or rivaroxaban placebo, for patients with moderate renal insufficiency, was used in 21% of patients in both groups. The primary efficacy and safety outcomes were consistent with the outcomes demonstrated with those who received full dose rivaroxaban.[12]

Apixaban

The ARISTOTLE trial represents the Phase 3 trial comparing the efficacy and safety of apixaban compared to warfarin in patients with NVAF.[13] Patients (n=18,201) were randomized in a double-blinded, double-dummy fashion to apixaban 5 mg twice daily or adjusted-dose warfarin. Patients considered to be at a high risk of bleeding based on at least two of the following risk factors; age ≥80 years, body weight ≤60kg, or serum creatinine ≥1.5 mg/dL, received a reduced dose of apixaban of 2.5 mg twice daily.

Patients receiving apixaban demonstrated a lower annualized rate of the primary endpoint compared to patients receiving warfarin (HR 0.79, 95% CI 0.66 – 0.95; p < 0.001 for noninferiority; p = 0.01 for superiority; Table 2).[13] Similar to the ROCKET-AF trial, there was a significant reduction in risk for hemorrhagic stroke among patients who received apixaban compared to warfarin without a reduction in ischemic stroke.

Major bleeding rates were lower in the apixaban group compared with the warfarin group (HR 0.69, 95% CI (0.60 – 0.80; p <0.001) (Table 3).[13] Similarly, major or CRNM bleeding occurred less frequently in patients who received apixaban than patients who received warfarin (HR 0.68, 0.61 – 0.75; p <0.001). Rates of other adverse events were similar between groups.

The reduced dose of apixaban of 2.5 mg twice daily was administered in 4.7% of patients in the apixaban group. The primary efficacy and safety outcomes were not significantly different for patients who received the 2.5 mg twice-daily dose compared to those who received the full dose.[13]

Edoxaban

Two doses of edoxaban were evaluated for efficacy and safety in patients with NVAF in the ENGAGE AF-TIMI 48 trial.[14] Patients (n=21,105) were randomized in a double-blind, double-dummy fashion to either high dose edoxaban (60 mg once daily), low dose edoxaban (30 mg once daily), or dose-adjusted warfarin. Patients randomized to edoxaban with moderate renal insufficiency (CrCl 30-50 mL/min), body weight of 60 kg or less, or concomitant use of a potent P-glycoprotein inhibitor, received 50% of their group allocation dose.

Both doses of edoxaban demonstrated noninferiority to warfarin in prevention of the primary endpoint (HR 0.79, 95% CI 0.63 – 0.99; p <0.001 for high dose, and HR 1.07, 95% CI 0.87 – 1.31; p = 0.005 for low dose) (Table 2).[14] Furthermore, edoxaban 60 mg daily demonstrated superiority (p = 0.02) to warfarin when the mITT population was analyzed, but this superiority was not maintained when the ITT population was tested (p = 0.08). Treatment with either dose of edoxaban led to significantly lower rates of hemorrhagic stroke compared with warfarin (HR 0.54, 95% CI 0.38 – 0.77; p <0.001 for high dose, and HR 0.33, 0.22 – 0.50; p <0.001 for low

Table 3: Safety of DOACs compared with warfarin in phase 3 trials in patients with NVAF[11-14]

	RE-LY			ROCKET AF		ARISTOTLE		ENGAGE AF – TIMI 48		
	Dabigatran							Edoxaban		
Outcome (%)a,b	110 mg	150 mg	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Low Dose	High Dose	Warfarin
Major bleeding p-value	2.71 p=0.003	3.11 p=0.31	3.36	3.6 p=0.58	3.4	2.13 p<0.001	3.09	1.61 p<0.001	2.75 p<0.001	3.43
CRNM bleeding p-value	13.2 p<0.001	14.8 p=0.005	16.4	11.8 p=0.35	11.4	2.08 p<0.001	3.00	6.60 p<0.001	8.67 p<0.001	10.2
Major or CRNM bleeding p-value	14.6 p<0.001	16.4 p=0.002	18.2	14.9 p=0.44	14.5	4.07 p<0.001	6.01	7.97 p<0.001	11.1 p<0.001	13.0
Intracranial bleeding p-value	0.23 p<0.001	0.30 p<0.001	0.74	0.5 p=0.02	0.7	0.33 p<0.001	0.80	0.26 p<0.001	0.39 p<0.001	0.85
GI bleeding p-value	1.12 p=0.43	1.51 p<0.001	1.02	3.2 p<0.001	2.2	0.76 p=0.37	0.86	0.82 p<0.001	1.51 p=0.03	1.23

DOAC=direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; CRNM=clinically relevant nonmajor bleeding; GI=gastrointestinal
a All p values for superiority.
b Event rate for RE-LY, ARISTOTLE, and ENGAGE AF are in %/year; for ROCKET AF, number/100 patient years

dose). While ischemic stroke was similar between patients receiving edoxaban 60 mg daily and adjusted-dose warfarin (1.25% for both), patients receiving edoxaban 30 mg daily demonstrated a significant increase in the incidence of ischemic stroke compared to warfarin (HR 1.41, 95% CI 1.19 – 1.67; p<0.001). This contributed to the lack of an FDA approval for the low dose edoxaban regimen.

Major bleeding was significantly decreased for both doses of edoxaban compared to dose-adjusted warfarin (HR 0.80, 95% CI 0.71 – 0.91; p <0.001 for high dose, and HR 0.47, 95% CI 0.41 – 0.45; p <0.001 for low dose) (Table 3).[14] Rates of CRNM bleeding and major plus CRNM bleeding were lower in patients receiving either dose of edoxaban compared to warfarin (Table 3). The incidence of other adverse effects were similar between the groups.

Rates of the primary endpoint in patients who received the 50% dose reduction were 2.32% for the high dose group (30 mg), 3.14% for the low dose group (15 mg), and 2.68% for patients with similar characteristics in the warfarin group.[14] These results were similar to those in the full dose groups. However, the reductions in the risk for major bleeding were significantly greater for patients in the high dose and low dose edoxaban groups who received a 50% dose reduction compared to those who did not (p = 0.02 and p <0.01 for interaction, respectively). Major bleeding rates for reduced-dose edoxaban patients were 3.05% for high dose group (30 mg) and 1.50% for low dose group (15 mg) compared to 4.85% for patients randomized to warfarin with similar characteristics. Additional post hoc analyses were performed with patients stratified by renal function. The rate of ischemic stroke increased with the use of edoxaban compared to warfarin in patients with CrCl >95 mL/min, likely due to lower plasma concentrations of edoxaban.[21] Therefore, edoxaban should not be used in patients with AF and a CrCl >95 mL/min.

Controversies and Discussion

A superficial review of the DOAC trial results may lead clinicians to conclude that one or more of these agents are a better selection compared to others when prescribing for patients. While this may be a tempting conclusion, it is critical that clinicians understand that details about differences in the study designs and study populations make comparisons extremely difficult.

Dosing is sometimes a reason for prescribing one agent over another. While the four currently available DOACs have a pharmacokinetic half-life of approximately 12 hours, dabigatran and apixaban are dosed twice daily, and rivaroxaban and edoxaban are dosed once daily.[20,22] For the vast majority of drugs used in clinical practice, the dosing regimens follow the pharmacokinetics. Therefore, a drug with a 12 hour half-life is dosed twice daily and a drug with a 20 hour half-live is dosed once daily. Despite the 12 hour pharmacokinetic half-live of rivaroxaban and edoxaban, these agents provide 24 hours of anticoagulant activity.[23-25] This is because the pharmacodynamic effect, the anticoagulant effect, is longer than the pharmacokinetic half-live. The ability of once daily dosing is most likely attributed to different target binding kinetics and volume of distribution between agents. Similarly, enoxaparin has a half-live of four to six hours, but is only dosed once or twice daily.[26,27] It has been assumed that the only way to get 24 hours of anticoagulant effect with a drug that has a 12 hour half-life is to provide much higher drug peak concentrations, and that these higher concentrations are then associated with higher risk for bleeding. Peak drug concentrations are relative to each individual agent, and are not comparable across agents. It has also been demonstrated in this class of agents that bleeding risk comes with agents having higher trough concentrations, and is not related to higher peak concentrations.[28,29]

The issue of dosing frequency can play an important role in patient adherence. It is unlikely that if a patient is nonadherent to therapy with warfarin that they would be adherent with a DOAC. Although, DOACs may be advantageous in patients where nonadherence is linked with the frequency of warfarin monitoring. One study across 103 anticoagulation clinic managed patients found that 11 patients were found to be nonadherent within 3 months of initiation of twice daily dabigatran. Adherence was defined as taking >80% or required doses.[30] There were also 30% of patients who reported missing doses during this time frame, with one reporting missing a dose every day. In a study of 5,736 Veterans Affairs patients, adherence of twice daily dabigatran demonstrated a connection to clinical outcomes.[31] Using the same definition of adherence as the previous study, 28% of patients were found to be nonadherent to twice daily dabigatran therapy. For every 10% decrease in adherence there was a corresponding 13% increased risk of stroke and all-cause mortality. Therefore, once daily DOAC therapy may be preferred to twice daily therapy in patients in whom adherence with a more complex regimen is unattainable. While there are no comparable data to evaluating adherence with once compared to twice daily DOAC therapy, adherence with once daily cardiovascular medications are typically better than twice daily medications.[32]

Renal elimination and perceived safety in patients with chronic kidney disease are cited as important differences among DOACs.

Table 4: Patient demographics and characteristics in the phase 3 clinical trials[11-14]

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Study Drug	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Patients (n)	18,113	14,264	18,201	21,105
Median age (years)	71 (mean)	73	70	72
Male sex (%)	64	60	65	62
Mean weight (kg)	83	28 kg/m^2 (BMI)	82 (median)	NR (10% ≤60 kg)
Low body weight (%)a	2.0	28	11	10
Paroxysmal AF (%)	33	18	15	25
Persistent or permanent AF (%)	67	81	85	75
CHADS2 score				
Mean	2.1	3.5	2.1	2.8
0-1 (%)	32	0b	34	–
2 (%)	36	13	36	77 (≤3)
3-6 (%)	32	87	30	23 (4-6)
Previous stroke or TIA (%)	20	55	19	28
Heart failure (%)	32	63	35	57
Diabetes mellitus (%)	23	40	25	36
Hypertension (%)	79	91	87	94
Previous VKA use (%)	50	62	57	59
Previous aspirin use (%)	40	37	31	29
Mean TTR (%)	64	55	62	65
Median TTR (%)	NR	58	66	68
Median follow-up (y)	2.0	1.9	1.8	2.8

AF = atrial fibrillation; NR = not reported; TIA = transient ischemic attack; VKA = vitamin K antagonist; TTR = time in therapeutic range
aFor RE-LY, <50kg; ROCKET AF, ≤70kg
b3 patients had a score of 1

The DOACs have varying dependence of renal function for their elimination. Dabigatran has the highest level of renal elimination at approximately 80%, followed by edoxaban at approximately 50%, rivaroxaban at approximately 36%, and apixaban at approximately 27%.[22-24] Importantly, the RE-LY, ROCKET AF, and ENGAGE AF trials[11,12,14] excluded patients with a CrCl < 30 mL/min, and the ARISTOTLE trial excluded patients with a CrCl < 25 mL/min.[13] Data in patients with lower CrCl is based on pharmacokinetic studies, and no patient outcome data is available. For some time it has been thought that apixaban was a safer agent in patients with renal disease due to the existence of data in patients receiving hemodialysis. This was a single dose study in eight patients that demonstrated a Cmax and area under the curve (AUC) that was not significantly different compared to patients without renal failure.[33] Similar data also exist with rivaroxaban. A single dose study of rivaroxaban 15 mg in eight patients undergoing chronic hemodialysis.[34] The findings demonstrated that the Cmax and AUC of this dose of rivaroxaban is not significantly different compared to patients with moderate renal insufficiency receiving the same dose. Clinicians should consider that these are both single dose studies without any clinical outcome information before using any of these agents in patients requiring hemodialysis.

In the individual studies, dabigatran and apixaban demonstrated superiority over warfarin in the ITT analysis, while rivaroxaban and edoxaban only demonstrated noninferiority in this analysis. So does this mean that, for example, apixaban should be used instead of rivaroxaban? A detailed understanding of the differences in study evaluation, design, and populations should be understood before considering the answer to this question. Rivaroxaban and edoxaban did demonstrate superiority over warfarin in the per-protocol and mITT analysis, respectively.[12,14] The difference between these analyses and the ITT analysis was only 28 patients in the ROCKET AF trial (0.2% of the total study population) and only 47 patients in the ENGAGE AF trial (0.3% of the total study population.[12,14] Small numbers of patients had an important impact of the statistical interpretation of results.

Differences demonstrated in the individual trials may also be simply an issue of trial size. While the trials with dabigatran, rivaroxaban, and edoxaban had approximately 6,000 to 7,000 patients per arm,[11,12,14] the ARISTOTLE trial with apixaban had over 9,000 patients per arm.[13] When evaluating the absolute difference in the primary endpoint between the ARISTOTLE and ROCKET AF trials, using the ITT analysis, the absolute difference is 0.3% in both trials (Table 2).[12,13] Therefore, was this same absolute difference superior for apixaban, and not for rivaroxaban, because apixaban is a better drug, or possibly due to the fact the ARISTOTLE trial had approximately 4,000 more patients than the ROCKET AF trial to evaluate the same primary endpoint? Statistical differences can be achieved by analysis of large patient populations but clinical differences may not be meaningful.

The issue of trial size likely also impacts the mortality findings from these trials. All of these trials produced a relative reduction in all-cause mortality of approximately 10%. The p-values for this reduction did not quite make statistical significance in the RE-LY (0.051),[11] ROCKET AF (0.07),[12] and ENGAGE AF (0.08)[14] trials, but was significant in the ARISTOTLE trial (0.047).[13] It then has to be decided if these findings suggest that apixaban is a better drug than the others, or that an additional 2000 patients per arm pushes the same relative reduction to become statistically significant. Based on the pharmacology among these agents, it would seem this is likely explained by differences in trial size. The reduction in mortality claim for apixaban has also been scrutinized by the FDA research site inspections. The ARISTOTLE trial received seven "official action indicated" reports from the FDA on the study sites.[35] These included issues with protocol, record keeping, patient safety, falsification of data, and inaccurate adverse drug event reporting. One site in China was found to have altered patient records.[35] If this site is removed from the full data set, the mortality findings are no longer statistically significant.[35]

The patients enrolled in these four clinical trials were not similar in regards to their risk of stroke and systemic embolism or bleeding (Table 4). In the RE-LY and ARISTOTLE trials, the mean $CHADS_2$ score was 2.2 and 2.1, respectively.[11,13] By comparison, patients in the ROCKET-AF and ENGAGE-AF trials were higher risk subjects with mean $CHADS_2$ score of 3.5 and 2.8, respectively.[12,14] Patients with a $CHADS_2$ score of 0 or 1, that may not be candidates for anticoagulant therapy,[36] made up about one-third of the total patients in RE-LY and ARISTOTLE. Only three patients in ROCKET-AF had this low level risk. Moreover, about one-third of patients in RE-LY and ARISTOTLE were high-risk, with a $CHADS_2$ score of ≥3. The ROCKET-AF trial enrolled 87% of patients in this high-risk group. Patients in RE-LY and ARISTOTLE consistently had lower incidence of all components of the $CHADS_2$ score compared to patients in ROCKET-AF and ENGAGE-AF (Table 4). Therefore, differences in patient populations studied are important to consider when evaluating these results, and make comparisons across agents and trials challenging.

In addition to differences in the patient populations studied, a recent reinterpretation of the DOAC phase 3 trials results suggest that the failure of rivaroxaban and high dose edoxaban to demonstrate superiority over warfarin in their ITT analyses of the primary efficacy endpoint may be due an imbalance of off-treatment events in the DOAC arms compared to the warfarin arms. These high discontinuation rates, coupled with more off-treatment events, would dilute the benefits of the treatment effect in the ITT analyses.[37]

It is important to realize that the benefit of all of the DOACs in the setting of NVAF is a significant reduction in hemorrhagic stroke (Table 2). Only dabigatran provided a significant reduction in the rates of ischemic stroke compared with warfarin.[11] In RE-LY, warfarin was administered in an open-label manner and INR was monitored and adjusted locally. In the other three trials, due to their double-bind, double-dummy designs, INR monitoring was done through standardized, encrypted, point-of-care devices that provide INR readings (real or sham) to the site investigators. This difference may result in greater variability in warfarin control at the individual patient level when warfarin is administered open-label compared to blinded, as demonstrated in an analysis of the Stroke Prevention Using Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III (open-label) and V (blinded) trials.[38,39] While the rate of stroke and SEE was 1.6% for ximelagatran in both studies, the efficacy outcome occurred in 2.3% of patients receiving open label warfarin in the SPORTIF III trial, but improved to 1.2% with blinded warfarin in the SPORTIF V trial.[38,39] Therefore, open-label warfarin resulted in a stroke and rate that was almost twice that of blinded warfarin.[38-40] Thus it may be that in RE-LY, there was greater individual INR variability which may have contributed to the higher ischemic stroke rate observed in the warfarin treatment group.[40]

The level of INR control within the trials has also been raised as an issue that may have impacted outcomes or interpretation of the data. The mean TTR for VKA therapy was highest in the ENGAGE AF trial (65%) and lowest in the ROCKET AF trial (55%), with both the RE-LY and ARISTOTLE trials being above 60% (Table 4). The reason for the lower TTR in the ROCKET AF trial is due to two factors. First, while investigators in the RE-LY, ARISTOTLE, and ENGAGE trials were provided guidance on warfarin management through protocols,[11,13,14] investigators in the ROCKET-AF trial were not provided protocols and managed warfarin according to their usual practice.[12] The other reason for the lower TTR is due to the difference in risk of patients mentioned above. It is known that higher risk patients and patients with more comorbidities have a more difficult time keeping their INR between 2.0 to 3.0.[41] The main concern with a lower TTR is the impact on efficacy and safety in the trial. In the RE-LY trial, the benefit of dabigatran over VKA was most evident in patients with the lowest quartile of TTR, while those in the highest quartile of TTR did not demonstrate a difference between the groups.[42] This was not evident with the direct Xa inhibitors rivaroxaban and apixaban. In both the ROCKET AF and ARISTOTLE trials, there was no correlation between the quartiles of TTR and efficacy and safety.[43,44] Therefore, the level of INR control did not impact the results of the trials, and the overall TTR should not be a factor when evaluating these trials.

The point of care INR monitoring device used in the ROCKET AF trial was recalled by the US FDA in December of 2014 after receiving almost 19,000 reports of malfunctions.[45] The device was found to report falsely low INR values for patients with anemia (hematocrit less than 30%), conditions associated with elevated fibrinogen levels (acute and chronic inflammatory conditions, severe infection, advanced cancer, or renal disease requiring dialysis), or patients bleeding or with unusual bruising.[46] The concern is that doses of warfarin could have been unnecessarily increased, putting these patients at higher risk of bleeding and making rivaroxaban appear safer than it really was.

Of the total safety population of the ROCKET AF trial (n=14,236) 37% of patients had at least one of the conditions mentioned in the device recall.[47] Therefore, the ROCKET AF investigators re-evaluated the data from the trial based on the presence or absence of one of these conditions to assess if patients with one of these conditions had an exaggerated safety response to rivaroxaban compared to warfarin. For major bleeding, the HR for all patients was 1.04 and was 1.18 for patients with any one of the recall conditions.[47] The results for ICH was similar, with a HR of 0.67 for all patients and 1.03 for those with any one of the recall conditions. If the device had led to unnecessary increases in warfarin dosing, then the HRs for the patients with any one of the recall conditions should have been lower than the overall study. That was not the case for any of the bleeding outcomes in the trial.[47] The European Medicines Agency has since concluded that "There is sufficient evidence to conclude that the benefit/risk balance remains unchanged and favourable for treatment with rivaroxaban in the prevention of thromboembolism in non-valvular atrial fibrillation".[48]

As mentioned above, the benefit of all of the DOACs compared to warfarin is a significant reduction in hemorrhagic stroke, which is counted as an efficacy and safety outcome in all of trials. When evaluating overall major bleeding, it is important to understand that the trials calculated the outcome of major bleeding over different periods of time. Apixaban and either dose of edoxaban significantly reduced major bleeding rates compared to warfarin, whereas rivaroxaban and dabigatran demonstrated similar rates of major bleeding compared to warfarin (Table 3). While this may be due to truly better safety with apixaban and edoxaban, it may also be due to how bleeding events were accrued. In the ARISTOTLE and ENGAGE-AF trials, bleeding events were only included if they occurred 2 or 3 days, respectively, after last dose.[13,14] In the RE-LY and ROCKET-AF trials, bleeding events were recorded over the duration of the study for both dabigatran and rivaroxaban.[11,12] Therefore, there is reason to question if there is truly a difference between the agents, or once again, is this more an issue of trial design.

Based on the controversies discussed here, it seems difficult to suggest that one agent has a defined benefit in efficacy or safely over another in patients with NVAF. Therefore, a collective review of these data as a class of agents may be most appropriate. A meta-analysis of all 71,683 participants in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF trials compared DOACs to warfarin.[8] Stroke or SEE were reduced by 19% by DOACs compared with warfarin (RR 0.81, 95% CI, 0.73 – 0.91; p <0.0001). DOACs significantly reduced all-cause mortality (RR 0.90, 95% CI, 0.85 – 0.95; p = 0.0003) and intracranial hemorrhage (RR 0.48, 95% CI, 0.39 – 0.59; p <0.0001), but increased gastrointestinal bleeding (RR 1.25, 95% CI, 1.01 – 1.55; p = 0.04).[8] Finally, in an analysis of the net clinical benefit of the DOACs compared to warfarin based on the phase 3 clinical trials, each of the drugs evaluated had a favorable net clinical benefit in comparison to warfarin.[49] All four DOACs had significant net clinical benefit for the composite of disabling stroke plus life

threatening bleeding.[49]

Conclusions

Current guidelines for the management of AF from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommend DOACs or warfarin for reduction of risk of thromboembolism in NVAF patients with a CHA_2DS_2-VASc score ≥2, with consideration of risk of stroke, risk of bleeding, and patient preferences.[50] These guidelines recommend a DOAC over warfarin only for patients who have difficult to manage INRs. In addition, the European Society of Cardiology ESC recommends that a DOAC be selected rather than a dose-adjusted VKA for most patients when oral anticoagulation is recommended.[51] This recommendation is based on the consistent reduction in hemorrhagic stroke demonstrated with all DOACs compared to therapy with a VKA.

When selecting a DOAC for reducing the risk of stroke in patients with NVAF, it is critical that clinicians have an in-depth understanding of the trial design, patient populations, and statistical evaluations. Based on existing data, it does not seem justified to claim that any agent has an efficacy or safety benefit compared to another. There are other individual patient factors to consider including risk factors, tolerability, patient preference, potential for drug interaction, and other clinical characteristics that may help with agent selection. Otherwise, only future prospective head-to-head clinical trials will answer this question.

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