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Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation: Pharmacology and Phase III Clinical Trials

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Abstract

Atrial fibrillation (AF) is a very common clinically significant arrhythmia noted in clinical practice. Its incidence increases with age and along with advanced age, other risk factors such as hypertension, vascular disease, heart failure, diabetes, prior stroke and female sex determine the associated stroke risk with AF. For over 40 years warfarin has been the drug of choice used to reduce this stroke risk associated with AF. However, the narrow therapeutic range, dietary restrictions, and chronic monitoring with warfarin led to the development of novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban. The purpose of this chapter is to elucidate pharmacology and the clinical performance of these NOACs in the setting of non-valvular atrial fibrillation (NVAf).

Keywords: novel oral anticoagulants, non-valvular atrial fibrillation, dabigatran, rivaroxaban, apixaban, edoxaban, stroke prevention, atrial fibrillation

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice affecting approximately 2.3 million people in the United States and 4.5 million people in Europe. The incidence increases with age and the prevalence being 9% between the ages of 80 and 90 [1]. Other risk factors include hypertension, coronary artery disease, chronic obstructive pulmonary disease, valvular heart diseases or surgeries, hyperthyroidism and chronic alcoholism. The mortality rate in AF is twice that of age-matched individuals in normal sinus rhythm, and stroke risk is increased approximately fivefold in patients with non-valvular atrial fibrillation (NVAf) [2].

Over the last five decades, vitamin K antagonists (VKAs) such as warfarin have been the only oral anticoagulants available for use as a long-term treatment to prevent strokes in patients with AF. Aspirin (ASA) may be used for patients with NVAf who cannot take warfarin for one reason or another, but ASA is much less effective than warfarin and is therefore recommended only for NVAf patients at low risk of stroke (CHA2DS2-VASc score of 0 or 1) in the American College of Chest Physicians (ACCP) guidelines [2–4]. The CHA2DS2-VASc score is an improvement on the CHADS2 score which has been widely used in clinical practice to risk stratify patients with NVAf for stroke. The CHA2DS2-VASc added three risk factors, namely age 65–74, female sex, and history of vascular disease [5]. However, the clinical trials for novel oral anticoagulants (NOACs) were conducted prior to widespread implementation of the CHA2DS2-VASc score, and thus, the risk stratification used in the trials is CHADS2.

Several historical placebo-controlled trials in subjects with AF were conducted with warfarin between 1989 and 1999. A meta-analysis of these historical trials using a fixed effects model showed that the relative risk reduction of stroke by warfarin was 62% (95% CI: 0.48, 0.72) with an absolute risk reduction of 2.7% for primary prevention and 8.4% for secondary prevention per year [2].

Although warfarin has been proven to be highly effective in preventing strokes, there have been multiple issues such as periodic monitoring, dietary restrictions, medication restrictions or interactions, and concerns for bleeding which render many patients with NVAf ineligible to receive warfarin therapy. For example, a registry of patients discharged from hospital revealed that only 54% of eligible AF patients received warfarin [6]. Likewise, surveys have indicated that many patients with AF cannot or will not take warfarin. Only 10% of patients with known AF who presented with an acute ischemic stroke had a therapeutic INR on admission, and even in those AF patients with a prior history of stroke or transient ischemic attack (TIA), only 18% had a therapeutic INR on admission [7]. Furthermore, studies show that the risk of intracranial hemorrhage was more than twice that of patients taking aspirin [2]. Thus, there was a need to develop an anticoagulant that would have similar or better efficacy as compared with warfarin along with better safety and more convenient management. Dabigatran, rivaroxaban, apixaban, and edoxaban have been approved over the past five years to satisfy this need.

2. Pharmacology

2.1. Mechanism of action

Dabigatran acts as a competitive reversible direct inhibitor of thrombin thereby preventing the thrombin-dependent conversion of fibrinogen to fibrin in the coagulation cascade. Rivaroxaban, apixaban, and edoxaban are direct competitive inhibitors of factor Xa, thereby inhibiting the formation of thrombin from prothrombin and downstream formation of fibrin from

fibrinogen. And since factor Xa is located at the top of the final common coagulation pathway, rivaroxaban, apixaban, and edoxaban can affect both the intrinsic and extrinsic coagulation cascades. These target coagulation factors and other pharmacological parameters for each drug are summarized in **Table 1**.

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Molecular weight (Dal)	724	436	460	738
Ki (nmol/l)	4.6	0.4	0.08	0.56
Concentration to double PT (µmol/l)	0.8	0.23	0.08	0.26
Concentration to double PTT (µmol/l)	0.23	0.69	7.4	0.51
Reversible binding	Yes	Yes	Yes	Yes
Reversal of antithrombotic effect	Specific antidote: Idarucizumab May consider PCC, APCC, rFVIIa	May consider PCC, APCC, rFVIIa	May consider PCC, APCC, rFVIIa	May consider PCC, APCC, rFVIIa
Half-life (h)	12–17	5–9	12	10–14
Cmax (h)	1	2–4	3–4	1–2
Volume of distribution (l)	50–70	~50	21	107
Protein binding	35%	92–95%	87%	55%
Renal excretion	80%	66%	27%	50%
Accumulation	None	None	None	None
Age effect	None	None	Yes [§]	None
Sex effect	None	None	None	None
Body weight effect	None	None	Yes	Yes
Effect of food	Yes*	Yes	None	None
Primary hepatic clearance pathway	No	CYP3A4	CYP3A4	No
Pregnancy category	C	C	B	C

* Increases Cmax to 2 h but does not affect bioavailability.

§ Dosage reduction recommended if two of the following three risk factors present: body weight <60 kg, age >80 years or serum creatinine >1.5 mg/dl.

Table 1. Pharmacokinetics and pharmacodynamics.

2.2. Absorption

Dabigatran itself is not absorbed via the oral route; however, its prodrug dabigatran etexilate is rapidly absorbed (bioavailability 3–7%) via the oral route and is converted to the active

ingredient by esterase-mediated hydrolysis in the liver. The absorption increases significantly when the capsules are broken, and thus, the capsules should not be broken or chewed or opened prior to administration. Additionally, when taken concomitantly with highly fatty food, the time to maximal concentration (C_{max}) increases from 1 to 2 h but the bioavailability is not affected [8]. Rivaroxaban is rapidly absorbed in the proximal intestine with maximum concentrations (C_{max}) appearing 2–4 h after tablet intake with the absolute bioavailability of 80% for the 10 mg dose and 66% for the 20 mg dose. The bioavailability is decreased when the drug is absorbed in the distal intestine or ascending colon [9]. This is an important consideration for patients with gastric bypass or other GI conditions that cause rapid transit. When taken with food, both the C_{max} and the bioavailability of rivaroxaban (for both 15 and 20 mg doses) increases by 39 and 76%, respectively [9]. Thus, it is recommended that rivaroxaban be taken with a large meal (ideally dinner) and not a light meal in order to slow down the transit time.

Unlike the first two, apixaban is absorbed throughout the gastrointestinal tract, and therefore, the drug displays a prolonged absorption which is not affected by food intake. The absolute bioavailability of apixaban is 50% for doses up to 10 mg with a C_{max} of 3–4 h. The distal small bowel and ascending colon account for 55% of the absorption of apixaban. Thereby, making it a better choice for patients with gastric bypass or other gastrointestinal conditions which lead to rapid transit, whereas in patients with colectomies or Crohn's disease, etc., apixaban's absorption may be altered and the drug may not be as readily available.

Edoxaban is also absorbed predominantly by the upper gastrointestinal tract with C_{max} of 1–2 h and bioavailability of 62%. The colon only accounts for 12% of absorption, thereby rendering the absorption of the drug susceptible to conditions that cause rapid transit, similar to rivaroxaban [10]. However unlike rivaroxaban, the absorption of edoxaban is not significantly affected by food intake.

2.3. P-glycoprotein transporter, cytochrome P-450 (CYP) enzymes, and drug interactions

The pro-drug dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (p-GP) transporter. And even though it neither induces nor inhibits p-GP, potential co-administration of other drugs that inhibit or induce P-GP can affect its bioavailability. The pharmacokinetics of dabigatran were not altered by another p-GP substrate digoxin, but an inhibitor like pantoprazole decreased the bioavailability by 30% [11]. Since H2 blocker ranitidine has no effect on the p-GP transporter, there was no effect on the area under the curve (AUC) when dabigatran was co-administered. For other p-GP inhibitors such as dronedarone or systemic ketoconazole, dosage adjustment was required in patients with reduced creatinine clearance (30–50 ml/min) [8]. Other p-GP inhibitors such as amiodarone and verapamil only modestly increased plasma concentrations (13 and 20%, respectively), and dose adjustment is not required for these medications [11]. On the other hand, potent p-GP inducers such as such as rifampin significantly reduced the AUC and C_{max} of dabigatran and concomitant use should therefore be avoided. Dabigatran is neither a substrate, nor an inducer or inhibitor of CYP enzymes [8].

Rivaroxaban is a substrate for p-GP transporter, CYP3A4/5 enzymes, and other transporters such as ATP-binding cassette G2 [9]. Approximately 51% of orally administered rivaroxaban is metabolized by the CYP enzymes 3A4 and 3A5. Thus, inhibition or induction of these proteins can lead to changes in the bioavailability of the drug. When studied with rifampin or phenytoin (p-GP and strong CYP3A4 inducers), the exposure to rivaroxaban decreased by 50%. Similarly, other combined strong p-GP, CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort should be avoided in patients taking rivaroxaban. For drugs that are combined p-GP and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, and erythromycin) or a moderate CYP3A4 inhibitor (fluconazole), studies showed increases in rivaroxaban exposure [9]. A dosage adjustment to 15 mg is required when taking these medications concomitantly in patients with decreased creatinine clearance (CrCl 15–50 ml/min). Additionally, rivaroxaban also has a low inhibitory effect on the p-GP transporter. Regardless, there were no significant interactions with 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of p-GP), and 20 mg once-daily dose of atorvastatin (substrate of CYP3A4 and p-GP) in healthy volunteers [12]. This is interesting because although neither dabigatran nor rivaroxaban has significant interactions with digoxin, rivaroxaban may be a better choice for patients with severe ischemic cardiomyopathy and NVAF because of an increased incidence of myocardial infarctions seen with dabigatran (discussed later).

Like dabigatran, apixaban is also a substrate for p-GP efflux transporter but unlike dabigatran, inhibition of p-GP transporter by itself does not affect the bioavailability. The drug is also metabolized by CYP3A4 and co-administration with drugs that are strong inducers and inhibitors for both p-GP and CYP3A4 increases the exposure to apixaban and raises the risk of bleeding. Rifampin, carbamazepine, phenytoin, and St. John's wort are strong combined inducers of p-GP and CYP3A4 and thus concomitant use should be avoided due to reduced exposure to apixaban. Ketoconazole, itraconazole, ritonavir, clarithromycin are strong dual inhibitors of p-GP and CYP3A4 and thus can increase exposure to apixaban [13]. Dose adjustment to 2.5 mg is recommended when apixaban is taken concomitantly with these medications. If the patient is already on the reduced dose (2.5 mg) of apixaban for other reasons, concomitant use of these medications is contraindicated [13]. Apixaban does not inhibit or induce p-GP and its potential to inhibit or induce CYP enzymes is minimal and as such the ability of apixaban to alter the exposure of co-administered drugs that are metabolites for these enzymes is minimal.

Unlike rivaroxaban and apixaban, CYP enzymes only account for 4% of the exposure to edoxaban. However, the intestinal p-GP transporter plays a significant role in clearance of the drug and thus inhibition of the transporter leads to increased exposure. Clinical interaction studies showed exposure to edoxaban increased by 87, 77, 53, 85, 73, 40, and 85% when used concomitantly with ketoconazole, quinidine, verapamil, erythromycin, cyclosporine, amiodarone, and dronedarone, respectively [10]. Subsequently in ENGAGE trial, the edoxaban was halved to 30 mg in patients who were taking verapamil, quinidine, or dronedarone [14]. And in the HOKUSAI VTE study, the dose was reduced for patients taking verapamil, quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, or ketoconazole [15]. The use of

edoxaban should be avoided when taking a potent p-GP inducer like rifampin, phenytoin, carbamazepine, and St. John's wort [16].

2.4. Elimination

In the phases II and III of the RE-LY trial, dabigatran was administered in oral, intramuscular, and intravenous formulations. After oral administration of radiolabeled dabigatran, 82.6–88.6% of radioactivity was recovered in the feces and 7% was recovered in the urine, the remaining was attributed to incomplete absorption of dabigatran. Renal clearance of intravenous dabigatran was approximately 80%. After infusion, the total clearance of dabigatran was found to be 92–141 ml/min, and the renal clearance was 81–106 ml/min showing that dabigatran is almost exclusively excreted via glomerular filtration and there was no secretion or reabsorption further down the tubule [7, 13]. The terminal half-life was 12–17 h in healthy individuals. The half-life was confounded by renal impairment and was increased to 15, 18, and 27.2 h, respectively, in mild (50–80 ml/min), moderate (30–50 ml/min), and severe (15–30) renal insufficiency. The total exposure (or AUC) also increased by approximately 1.5-, 3.2-, and 6.3-fold in mild, moderate, and severe renal impairment, respectively, when compared to normal renal function. It is thus recommended that the dose of dabigatran for atrial fibrillation be halved to 75 mg when the creatinine clearance (CrCl) is between 15 and 30 ml/min for and the use of dabigatran should be avoided in patients with CrCl less than 15 ml/min or those on dialysis [8]. Administration of dabigatran in patients with moderate (Child-Pugh class B) liver impairment showed large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics because the primary elimination pathway for dabigatran is via the kidneys [8].

Off the orally administered radiolabeled rivaroxaban, 66% was recovered in the urine (36% unchanged) and 28% was recovered in the feces (7%). The renal excretion of rivaroxaban is primarily driven by active tubular secretion and secondarily by glomerular filtration in a 5:1 ratio. The terminal half-life is 5–9 h in healthy young individuals [9, 12]. Like dabigatran, the exposure to rivaroxaban also increases by 44% for mild, 52% for moderate, and 66% for severe renal impairment. As such, it is recommended that the dose of rivaroxaban for stroke prevention in NVAf be reduced to 15 mg orally with dinner in patients with moderate-to-severe renal impairment (CrCl 15–50 ml/min) due to increased exposure and rivaroxaban should be avoided in patients with CrCl <15 ml/min or those on dialysis. Rivaroxaban was not studied in patients with severe (Child-Pugh class C) hepatic impairment, and exposure to rivaroxaban increased by 15 and 127% in patients with Child-Pugh class A and B hepatic impairment [9].

Unlike dabigatran and rivaroxaban, apixaban is excreted in both urine and feces. Renal excretion accounts for 27% of total clearance and biliary, and direct intestinal excretion accounts towards the fecal elimination of apixaban. The terminal half-life is 12 h, and the exposure is not significantly affected (<1.5× normal) for any level of renal impairment including end-stage renal disease. Thus, no dosing adjustment is recommended kidney disease alone. However, a dosage reduction of apixaban to 2.5 mg is recommended in patients that meet another one of the following two risk factors: age >80 years or body weight <60 kg [13]. However, it should be noted that patients with end-stage renal disease (CrCl <15 ml/min) were

not studied in the clinical efficacy and safety trials [16]. The recommendation for no dosage adjustment is based on pharmacokinetic data showing a modest 17% increase in apixaban exposure in patients receiving hemodialysis with an elimination via dialysis of 18 ml/min reducing exposure of the drug by 14% postdialysis as compared to off dialysis period. Similarly, in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, the area under the curve or exposure did not change significantly as compared to normal individuals and no dose adjustment is necessary in patients with Child-Pugh class A hepatic impairment. However, since patients who have Child-Pugh class B hepatic impairment may have intrinsic coagulation abnormalities, a recommendation on dosing cannot be made due to limited clinical experience. Like the others, use of apixaban is not recommended in patients with severe (Child-Pugh class C) hepatic impairment [13].

Edoxaban is excreted as unchanged drug in the urine with renal clearance accounting for 50% of total clearance. Metabolism as well as biliary and intestinal excretion accounts for the remaining clearance. The terminal half-life is 10–14 h. In a pharmacokinetic study, the total systemic exposure to edoxaban increased by 32, 74, and 72% in patients with mild (50–80 ml/min), moderate (30–50 ml/min), severe (15–30 ml/min) renal impairment, and by 93% in patients receiving dialysis. Thus, a reduction in dose to 30 mg daily is recommended in patients with CrCl 15–50 ml/min for stroke prevention in non-valvular atrial fibrillation [10, 16]. Interestingly, the incidence of stroke was higher in patients receiving edoxaban who had a CrCl >95 ml/min as compared to warfarin in the clinical trial and the use of edoxaban is not recommended in these patients [10, 14]. There were no significant differences for edoxaban in patients with mild or moderate (Child-Pugh class A or B) hepatic impairment. A dose adjustment is not necessary for Class A patients; however, once again due to the intrinsic coagulation abnormalities in patients with class B hepatic impairment, the use of edoxaban is not recommended [16].

2.5. Special populations

The pharmacokinetics and pharmacodynamics of both dabigatran and rivaroxaban are not affected by age, gender, or body weight. There is no effect of ethnicity on the pharmacology of dabigatran either, but rivaroxaban did have 20–40% higher exposure in patients of Japanese ethnicity as compared to other ethnicities including Chinese [9]. This exposure was reduced when it was corrected for body weight, but further studies may be required to assess clinical implications to the use of rivaroxaban in the Japanese population specifically. Although individually aged over 80 years and body weight <60 kg only modestly increased the exposure to apixaban (<1.5× normal individuals), the combination of the two risk factors was deemed to have a significant increase in the exposure of the drug. Thus, a reduced dose of 2.5 mg was used in ARISTOTLE for patients who had two of the following three risk factors: age older than 80 years, body weight <60 kg, and creatinine >1.5 mg/dl [13, 17]. Age is not a risk factor for increased exposure of edoxaban but a phase II open-label study done in Japan revealed that patients with total body weight <60 kg had double the bleeding risk as compared to patients with total body weight >60 kg. Thus, in the phase III clinical trial, the dose of edoxaban was reduced to 30 mg daily in patients with total body weight <60 kg [14, 16].

Dabigatran, rivaroxaban, and edoxaban are all under category C for pregnancy. Animal studies showed increased maternal bleeding and increased fetal mortality with all three drugs. There was decreased fetal implantation with dabigatran, and increased post-implantation loss, and decreased fetal weight with rivaroxaban and edoxaban [8, 9, 16]. Additionally, there was decrease in gall bladder size or absence of the organ with the use of edoxaban in animal studies. Ten pregnancies were reported during the HOKUSAI VTE study, from which there were four full-term births, two preterm births, one spontaneous abortion in the first trimester, and three elective terminations during the study [15, 16]. In comparison, animal studies with apixaban did not cause an increase in fetal toxicity, malformations, or mortality. There was an increase in the rate of maternal bleeding at the rate of 19, 4, and 1 times, respectively, for mice, rats, and rabbits with apixaban. As a result, the use of apixaban is under category B for pregnancy [13]. None of the NOACs are recommended for mothers who are breastfeeding, and the use of these drugs has not been studied in the pediatric population.

3. Clinical trials

3.1. Trial designs

The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial was designed as a non-inferiority trial to compare dabigatran to warfarin in 18, 113 patients from 951 clinical centers in 44 countries. Two doses of dabigatran; 110 and 150 mg were administered in a double-blinded fashion [18]. We will discuss the data for the 150 mg dose of dabigatran as FDA approval was only obtained for 150 and 75 mg (not studied) doses. The warfarin arm was not blinded because the patients taking it needed regular follow-ups for INR control. The semi-blinded design of RE-LY could leave the trial open to reporter bias. Thus, the authors of the trial tried to minimize this bias by assigning two independent investigators who were unaware of the treatment assignments, to adjudicate each event. In addition, all hospital records were reviewed to ensure that all events were detected and correctly documented [18]. In contrast, the other three trials were designed in a double-blinded double dummy randomized fashion to avoid reporter bias.

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 studied Warfarin in comparison with 20 mg of rivaroxaban in 14,264 patients from 1178 centers in 45 countries [19]. Similarly, the apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study enrolled 18,201 patients at 1034 sites in 39 countries and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) enrolled 21,105 patients from 1393 centers in 46 countries to study apixaban 5 mg and edoxaban 60 mg to warfarin, respectively [14, 17].

Lower doses of NOACs were studied in ROCKET, ARISTOTLE, and ENGAGE. Rivaroxaban 15 mg was used for patients with creatinine clearance 15–50 ml/min [19]. For ARISTOTLE,

apixaban dose was reduced to 2.5 mg twice daily if the patient had two of the following three risk factors for increased bleeding: age ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine level ≥ 1.5 mg per deciliter [17]. In ENGAGE, randomization was done in 1:1:1 fashion for warfarin, edoxaban 60 mg, and edoxaban 30 mg. The doses of edoxaban were further halved to 30 and 15 mg for patients who either had a creatinine clearance 30–50 ml/min or body weight ≤ 60 kg thereby allowing a range of doses from 15 to 60 mg to be used in the study [14]. However, the results of the study were more promising from the 60 mg dose with reduction to 30 mg for specific patients leading to FDA approval. Thus, for the scope of this chapter, only the results pertaining edoxaban 60 mg daily dose will be discussed.

Additionally, ROCKET-AF used both intention-to-treat and on-treatment analyses, and the outcomes listed as number of events per 100 patient-years (instead of percent per year) [19]. To facilitate comparisons between trials, only the intention-to-treat analyses are reported in this chapter. Similarly, ENGAGE also had a prespecified intention-to-treat analysis to assess superiority to warfarin which was not statistically significant and thus will not be discussed for the purposes of this chapter.

3.2. Patient populations

All four trials used similar criteria for enrolling and following patients with subtle differences as listed in **Table 2**. However, these subtle differences may affect decision-making in different clinical scenarios. For example, only ENGAGE included patients with prior bioprosthetic valve or valve repair and as such edoxaban may be the preferred agent for stroke prevention in these patients. Similarly, for newly diagnosed strokes, ARISTOTLE excluded patients with strokes within 7 days of randomization. RE-LY, ROCKET, and ENGAGE excluded patients with strokes within 6, 3, and 1 month, respectively. RE-LY and ROCKET also excluded patients with transient ischemic attack (TIA) within 14 days and thus if a patient has had a stroke more than 7 days prior to and within 1 month of planned anticoagulation, apixaban may be the preferred agent. ARISTOTLE also included patients with creatinine clearance less than 30 ml/min and had the most patients in this category. As such in the absence of other risk factors for bleeding and increased exposure to apixaban, the use of apixaban would be preferred in these patients.

Another important consideration is the CHADS₂ score used in the trial, because higher scores are associated with incrementally higher risk of stroke. Both ROCKET and ENGAGE required a minimum CHADS₂ score of 2 to be included in the trial. Additionally, ROCKET also permitted patients with lower left ventricular ejection fractions, thus enrolling a higher risk patient population than RE-LY and ARISTOTLE. Roughly one-third of patients in RE-LY and ARISTOTLE had CHADS₂ scores of 0 or 1, resulting in an overall 1% lower absolute risk of stroke in those patients as compared to those enrolled in ROCKET or ENGAGE. Even though the CHADS₂ score was evenly distributed between the drug and warfarin groups were evenly distributed in both trials, the overall incidence of primary outcome could be overestimated for the ROCKET and ENGAGE trials.

Characteristic	RE-LY	ROCKET	ARISTOTLE	ENGAGE
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosing	150 mg BID (75 mg)	20 mg daily (15 mg)	5 mg BID (2.5 mg)	60 mg daily (30 mg)
Total population (N)	18,113	14,266	18,206	21,105
Design	PROBE	Double blinded	Double blinded	Double blinded
Primary efficacy endpoint	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Primary safety endpoint	Major bleeding	Major bleeding or clinically relevant non-major Bleeding	Major bleeding	Major bleeding
VKA naïve	50%	38%	43%	41%
Mean TTR for INR during study	64	55	62	68
<i>Inclusion criteria</i>				
AF criteria	AF at screening or within 6 months	AF recorded in 30 days prior to randomization and within 1 year	2 episodes of AF or flutter recorded 2 weeks apart within 1 year	AF recorded within 1 year
LVEF	40% or less	35% or less	40% or less	NA
<i>Exclusion criteria</i>				
Valve disease	Hemodynamically significant or prosthetic	Hemodynamically significant or prosthetic	Moderate-severe mitral stenosis or prosthetic	Moderate-severe mitral stenosis or mechanical [§]
Stroke	Severe w/in 6 months or TIA w/in 14 days	Severe w/in 3 months or TIA w/in 14 days	Stroke w/in 7 days	Stroke w/in 30 days
Bleeding	Surgery w/in 30 days, GI bleed w/in 12 months, any intracranial bleed, severe hypertension	Surgery w/in 30 days, GI bleed w/in 6mo, active internal bleeding, any intracranial bleed, dual antiplatelet therapy, severe hypertension, platelet \leq 90,000	Any intracranial bleed, dual antiplatelet therapy, severe hypertension	High risk for bleeding, dual antiplatelet therapy
<i>Patient demographics</i>				
Age (yrs)	71	71	70	72

Characteristic	RE-LY	ROCKET	ARISTOTLE	ENGAGE
Male gender (%)	63.2	60.3	64.5	61.9
<i>Type of atrial fibrillation (%)</i>				
Paroxysmal	32.6	17.5	15.1	25.4
Persistent/ permanent	67.4	82.5	84.9	74.6
<i>CHADS₂ score (%)</i>				
I	32.2	0	34	0
II	35.2	13	35.8	46.8
III–VI	32.6	87	30.2	53.2
<i>Comorbidities (%)</i>				
Hypertension	78.9	74	87.3	93.6
Previous TIA	20.3	54.9	19.2	28.3
Diabetes	23.1	40.4	25	36.2
Heart failure	31.8	62.6	35.5	57.5
Prior MI, CAD, CABG	28	17.3	14.5	33.3
<i>Medications (%)</i>				
ACE or ARB	66.7	55.1	70.9	65.9
Beta-blockers	63.7	65.1	63.6	66.3
Digoxin	28.7	38.8	32	30
Amiodarone	10.9	NA	11.1	11.8
Statins	43.9	42.9	45	47.8
Gastric antacids	17.9*	NA	18.5	NA
NSAIDS	1.4	NA	8.2	1.1
Aspirin	38.7	36.3	31.3	29.3
Thienopyridine	5.5	NA	1.9	2.3
<i>Creatinine clearance (%)</i>				
>80 ml/min	32	32.2	41.2	37.2
>50–80 ml/min	47.4	46.7	41.9	43
>30–50 ml/min	19.7	21.1	15	18.4
<30 ml/min	0.005	NA	1.5	0.76

* Total of proton pump inhibitors 13.9% and H₂ antagonists 4%.

§ Bioprosthetic valves or valve repair patients were included.

Table 2. Study design and patient demographics.

3.3. INR control

INR control is probably the most important factor in determining the non-inferiority of NOACs. All trials used the Rosendaal method of total time in therapeutic range (TTR, reflecting the percent of time the patient had an INR between 2 and 3) [20]. Overall, the TTR was 64% in the RE-LY trial, 55% in ROCKET, 62% for ARISTOTLE, and 68% for ENGAGE. These numbers clearly reflect that ROCKET had the least robust INR control in the warfarin arm leading to significant criticism of the trial.

Although these data were not analyzed further in the primary publications, the heterogeneity of INR management in the other trials appeared to impact clinical outcomes. In RE-LY, the INR control in east and South-East Asia was worse than centers in Europe and North America. The hazard ratio for major bleeding with dabigatran 150 mg was 1.24 ($p = 0.03$) when the TTR was 68% or more [11]. Additionally, higher rates of both thromboembolic events and major bleeds were seen with warfarin in centers with TTR $<57\%$, even after adjusting for multiple other potential confounding variables [21]. The inadequacy of INR control in Asia may explain the more robust performance of dabigatran in those centers. Dabigatran 150 mg also performed better than warfarin for a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death with a hazard ratio of 0.64 for TTR <57.1 and hazard ratio of 1.19 for TTR >72.6 ($p = 0.006$). This trend was mirrored in the mortality rate where dabigatran had an advantage at the centers with poor INR control (HR 0.67 vs 1.08, $p = 0.052$) [21].

Similar to dabigatran, edoxaban also had lower efficacy in patients with higher TTR. The hazard ratio for edoxaban 60 mg vs warfarin in TTR <57.7 was 0.8 compared to hazard ratio of 1.07 for patients with TTR >73.9 . TTR [10]. A different issue was noted in ROCKET-AF, the TTR was low for the trial overall trial, and the resultant bleeding risks were equivalent between rivaroxaban and warfarin. However, the centers in the USA where TTR was around 64%, patients taking rivaroxaban suffered 2.5–3.7 more bleeds per stroke prevented as compared to those taking warfarin [12]. Overall in patients with excellent INR control, warfarin may still be the drug of choice for stroke prevention in atrial fibrillation.

3.4. Results and discussion

The primary outcome in all four trials was stroke or systemic embolism, and the primary safety endpoint was major bleeding (RE-LY, ARISTOTLE, and ENGAGE), or combined major and clinically important non-major bleeding events (ROCKET). As illustrated in **Table 3**, patients randomized to the 150 mg dose of dabigatran in RE-LY had a reduction in the primary outcome, experienced fewer ischemic as well as hemorrhagic strokes, and had a strong trend toward lower all-cause mortality in spite of experiencing higher rates of myocardial infarction [18]. This trend for higher myocardial infarction leads to several meta-analyses which showed approximately 30–40% increase in the rates of myocardial infarction with the use of dabigatran as compared to control arms including enoxaparin, placebo, and warfarin [22, 23]. However, in a post market analysis of 134,000 Medicare patients over 65 years of age done by the FDA did not show any difference between the incidence of myocardial infarction between Dabigatran (15.7 per 1000 person years) and warfarin (16.9 per 1000 person years, $p = 0.92$) [24]. None

Clinical outcome	RE-LY				ROCKET				ARISTOTLE				ENGAGE			
	Dabiga- tran 150 mg BID, %/y	Warfar- in %/y	Hazard ratio	p value	Rivaroxa- ban 20 mg QD, %/y	Warfar- in %/y	Hazard ratio	p value	Apixa- ban 5 mg BID, %/y	Warfar- in %/y	Hazard Ratio	p value	Edoxa- ban high dose %/y	Warfar- in %/y	Hazard Ratio	p value
Stroke or SAE	1.11	1.69	0.66	<0.001	2.1	2.4	0.88	<0.001	1.27	1.6	0.79	0.01	1.18	1.5	0.79	<0.001
Stroke	1.01	1.57	0.64	<0.001	1.65	1.96	0.85	0.092	1.19	1.51	0.79	0.01	0.26	0.47	0.54	<0.001
Ischemic	0.92	1.2	0.76	0.03	1.34	1.42	0.94	0.581	0.97	1.05	0.92	0.42	1.25	1.25	1	0.97
Hemorrhagic	26.1	0.38	0.26	<0.001	0.26	0.44	0.59	0.024	0.24	0.47	0.51	<0.001	0.26	0.47	0.54	<0.001
Disabling	0.66	1	0.66	0.005	0.39	0.5	0.77	0.188	0.5	0.71	0.71	0.94	0.28	0.3	0.94	0.75
Non-disabling	0.37	0.58	0.62	0.01	0.79	0.77	1.03	0.863					0.81	1.01	0.8	0.044
Myocardial in- farction	0.74	0.53	1.38	0.048	0.91	1.12	0.81	0.121	0.53	0.61	0.88	0.37	0.7	0.75	0.94	0.6
Death from vascular cause	2.28	2.69	0.85	0.04	1.53	1.71	0.89	0.289								
All-cause mor- tality	3.64	4.13	0.88	0.051	1.87	2.21	0.85	0.073	3.52	3.94	0.89	0.047	3.8	4.35	0.87	0.006
Major bleeds	3.11	3.36	0.93	0.3	3.6	3.4	1.04	0.58	2.13	3.09	0.69	<0.001	2.75	3.43	0.8	<0.001
Intracranial bleeds	0.3	0.74	0.4	<0.001	0.5	0.7	0.67	0.02	0.33	0.8	0.42	<0.001	0.38	0.85	0.47	<0.001
GI bleeds	1.51	1.02	1.5	<0.001	3.15*	2.16*		<0.001	0.76	0.86	0.89	0.37	1.51	1.23	1.23	0.03

* Gastrointestinal bleeds in ROCKET-AF were reported as percentages and no Hazard ratio was reported, whereas all other outcomes in this trial were reported as number per 100 patient-years.

Table 3. Efficacy outcomes.

of the other NOAC had any signal towards myocardial infarction in their respective trials and the choice of using an alternative agent to dabigatran in the setting of known coronary artery disease should be individualized based on the clinical setting and physician discretion. There was no difference in overall major bleeding, where a significant reduction in intracranial hemorrhage was offset by a significantly higher rate of gastrointestinal bleeding.

For the intention-to-treat analyses in ROCKET-AF, rivaroxaban was noted to be non-inferior (but not superior) to warfarin in reducing the primary endpoint [19]. The reduction in ischemic stroke was not statistically significant as compared to the warfarin group and the outcomes were driven by a significant reduction in hemorrhagic stroke by rivaroxaban which may be reflective of the poor INR control in the trial. There was a trend toward reducing all-cause mortality in ROCKET, and like RE-LY, an equivalent bleeding endpoint was driven by a significant reduction of intracranial hemorrhage in the setting higher rates of gastrointestinal bleeds. In comparison, apixaban was the only drug to show statistically significant reduction in primary outcome compared to warfarin in both non-inferiority and superiority analyses. And, like the other trials, the reduction in the primary outcome was driven by a significant reduction of hemorrhagic strokes [17]. ENGAGE did show non-inferiority to warfarin in the reduction of primary outcomes, but in the prespecified superiority analysis, the difference was not statistically significant [14]. Unlike the prior studies of dabigatran and rivaroxaban, both ARISTOTLE and ENGAGE demonstrated a statistically significant reduction in all-cause mortality and major bleeding with the study drugs in comparison to warfarin [14, 17]. However, only apixaban showed no significant increase in gastrointestinal bleeding among all NOACs and it should be considered as the agent of choice in patients with prior (or at high risk for) gastrointestinal bleeding.

4. Conclusion

The approval of NOACs for stroke prevention in patients with NVAf has ushered a new era in this field with a multitude of options available for practitioners. Warfarin still may be the drug of choice in several clinical situations such as compliant patients with good INR control or those with valvular heart disease, etc. However, patient preference and the ease of use have made NOACs the preferred initial agent for stroke prevention in patients with NVAf. The subtle differences between the NOACs described throughout this chapter are aimed at providing an improved understanding of the intricacies with which these medications perform in the human body and thereby help guide decision-making.

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