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Research Article

Atrial fibrillation, Stroke and the Use of Novel Oral Anticoagulants: A Review of Phase III Randomized Clinical Trials

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ABSTRACT

Atrial Fibrillation (AF) significantly increases the risk of stroke, a leading cause of death and disability. Anticoagulation therapy, traditionally with warfarin, effectively reduces stroke risk but is limited by the need for frequent monitoring to maintain therapeutic international normalized ratio (INR). Novel Anticoagulants (NOVACs), including Direct Thrombin Inhibitors (DTIs) and Direct Factor Xa Inhibitors (DFXaIs), have emerged as promising alternatives. This review examines phase III Randomized Clinical Trials (RCTs) assessing NOVACs for stroke prevention in AF patients compared to warfarin. The RE-LY trial evaluated dabigatran, finding that a low dose (110 mg twice daily) had comparable efficacy to warfarin in reducing stroke and systemic embolism but with a lower risk of major hemorrhage. A higher dose (150 mg twice daily) showed superior efficacy in reducing stroke and systemic embolism but had similar bleeding rates. The ROCKET-AF trial found rivaroxaban (20 mg once daily) comparable to warfarin for stroke prevention and major hemorrhage risk. The ARISTOTLE trial demonstrated that apixaban was superior to warfarin in reducing both stroke/systemic embolism and major bleeding events. Overall, NOVACs offer at least comparable safety and efficacy profiles to warfarin and may be preferred when monitoring anticoagulation effects is impractical. While NOVACs demonstrate promise, generalized phase IV RCTs are recommended to compare their long-term safety and efficacy, with warfarin remaining a benchmark for stroke prevention in AF.

Keywords: Dabigatra; Apixaban; Rivaroxaban; Atrial fibrillation; Novel anticoagulants; Clinical trials

INTRODUCTION

Atrial Fibrillation (AF) is the most common type of cardiac arrhythmia, which increases the risk of ischemic stroke fivefold [1,2]. Among the major causes of stroke, AF may account for 45% of all embolic strokes and it was estimated that up to 15%-20% of patients admitted with all strokes were diagnosed with AF [3-5]. As a result of blood stasis due to the disruption of normal electromechanical atrial function, the chance of clot formation increases, leading to embolic phenomena, including stroke. Prevention of stroke associated with AF forms a global public health priority, as it is common and frequently devastating (70%-80% links to death or disability). However, it is can be preventable using anticoagulants, which result in around 64% stroke-risk reduction and 25% mortality lowering [6,7]. Therefore, antiplatelet or anticoagulation therapy should be considered in all patients with AF, regardless of whether or not normal sinus rhythm is restored [8]. The American College of Chest Physicians (ACCP) recommends the CHADS2 stroke risk estimator to determine whether patients should receive antiplatelet or anticoagulant therapy. According to the CHADS2 score, which is an evaluation tool, a patient receives one point for having diabetes mellitus, hypertension, congestive heart failure, or being 75 years of age or older and two points for having a past history of stroke or Transient Ischemic Attack (TIA). The total CHADS2 score is given out of 6 and it may be used to measure AF patients risk of developing stroke and determine whether they may benefit from anticoagulation therapy. This tool has also been utilized to determine eligibility for several Randomized Clinical Trials (RCTs) studying Novel Anticoagulants (NOVACs) [8,9].

For over 60 years, vitamin K antagonists have been used as the standard therapy in stroke prevention [10]. Warfarin resulted in an estimated stroke and systemic embolism reduction of more than 60% [11]. However, its use was associated with treatment discontinuation and poor adherence due to major bleeding, which has an estimated annual rate of 2.3% among patients receiving warfarin for prophylaxis against stroke [12]. Warfarin therapy is also complicated by its frequent International Normalized Ratio (INR) monitoring, slow onset of action, narrow therapeutic index, variable pharmacokinetics, food and drug interactions and INR-

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based dose adjustment [13,14]. Therefore, due to the recent advent of NOVACs, their application in the domain of stroke reduction is still under review because of their potential to overcome the various limitations associated with vitamin K antagonists [15,16].

The newly introduced anticoagulants can dramatically change thromboembolic risk management. The two important NOVAC categories: Direct Thrombin Inhibitors (DTIs) and Direct Factor Xa Inhibitors (DFXaIs), as listed in Figure 1, rely on targeting a single coagulation factor. Both thrombin (factor IIa) and factor Xa play central roles in the common coagulation pathway [17-19]. Inhibition of either enzyme prevents coagulation initiated by either the intrinsic or extrinsic pathway [20,21].

NOVACs have a number of beneficial pharmacologic characteristics that may improve therapeutic outcomes in treating thromboembolic conditions (Table 1). They have been found to produce comparable effectiveness and an improved safety profile, as compared to warfarin [22]. A major concern about their use is their ability to balance the beneficial outcomes of preventing thromboembolic events with the undesirable outcomes from haemorrhagic stroke.

Routine laboratory monitoring is less frequently observed with NOVACs. In relation to liver function, unlike warfarin, their pharmacokinetic behavior does not require strict dosage adjustment, as fewer drug or food interactions occur. However, their monitoring is mostly dependent on renal function. Unfortunately, no antidote has been introduced [8].

Among the most current recommendations, the Canadian Cardiovascular Society (CCS) and the American College of Cardiology (ACC) Foundation consider the use of dabigatran as a preferable agent over warfarin [23]. Rivaroxaban and apixaban are major DFXaIs available with the most current use recommendation in the USA. They are among the Food and Drug Administration (FDA)-approved NOVACs for preventing stroke and systemic embolism in adult patients with AF [16]. These newer agents were incorporated in professional guidelines, including the 2012 ACCP evidence-based guidelines that prioritize the use of dabigatran before warfarin in patients who require anticoagulation for preventing AF-stroke and are known to have a CHADS2 score of ≥ 1.

Apart from other studied NOVACs, the reversible DTI dabigatran offers several preferable pharmacologic properties, encouraging its use for treating various thromboembolic conditions. Among the most important ones, dabigatran is capable of avoiding metabolism by hepatic CYP450, thus resulting in minimal or no interactions with food or drugs. Other pharmacologic features promoting the use of dabigatran as a therapeutic option include its rapid onset of action, wide therapeutic index and effective-safe use. Furthermore, dabigatran requires no routine laboratory monitoring and it can be given in a fixed dose [24-32]. Also, rivaroxaban and apixaban represent a new and promising anticoagulation, as they were found to exhibit predictable pharmacokinetic behavior. Doses from these two agents rarely need to be adjusted, even when extreme demographic factors are taken into account [33].

In this review, we provided an illustration from completed phase III RCTs comparing the NOVACs dabigatran, rivaroxaban and apixaban to warfarin for the effective-safe use among patients with AF and at potential risk of thromboembolic events. In addition, some pharmacologic features forming a challenge regarding the administration of the selected drugs are also highlighted.

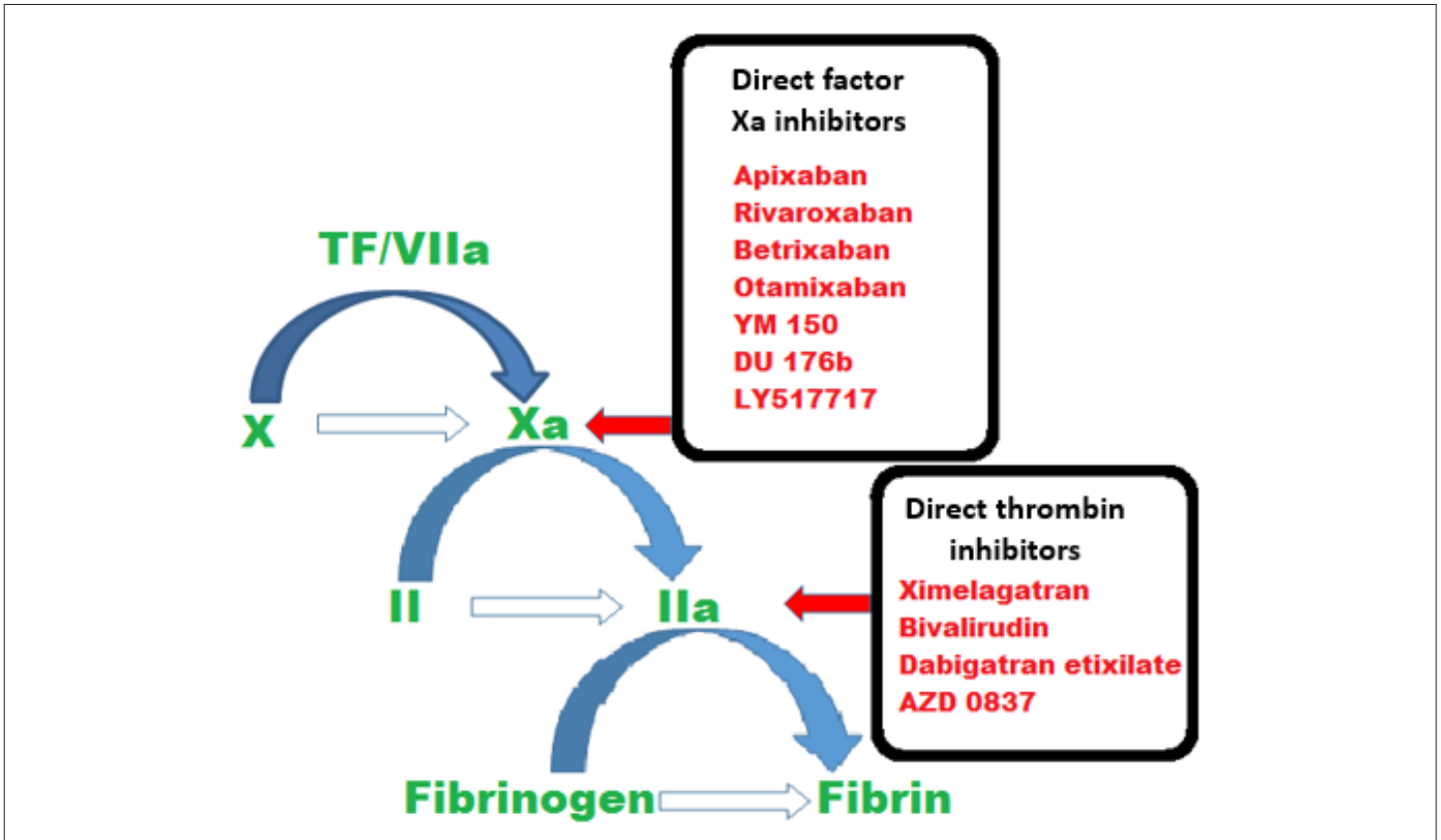

Figure 1: The two major categories of NOVACs: Direct Thrombin Inhibitors (DTI) and Direct Factor Xa Inhibitors (DFXaIs) and their selective inhibitory effect on coagulation factors in the coagulation cascade.

Table 1: Comparison of pharmacologic characteristics between the major NOVACs (DFXaIs and DTIs) used in AF-associated stroke prevention and warfarin.

Category	Drug	Mechanism of action [23]	Dose in AF/ t1/2 hours [8], [23-28]	Metabolism/ Monitoring [23,24,28]	Clinical therapeutic indications [23,29]	Common side effects [8,17,23]	Antidote [30], [31]	RCTs Approval [23]
Vitamin K antagonists	Warfarin	Vitamin K epoxide reductase inhibitor	INR-adjusted/ t1/2=40 hrs	Hepatic, mainly *via* CYP2C9, CYP1A2, CYP3A4, CYP2C8, CYP2C18 and CYP2C19 / INR-adjusted	Stroke prevention in NVAF patients, prevention of clots formation in VTE/PE and in the presence of artificial heart valves.	Major bleeding with 2.3% annual rate.	Vitamin K	Approved
DFXaIs	Apixaban	Inhibits unbound and clot bound factor Xa	5 mg twice daily or 2.5 mg twice daily if (age ≥ 80 years, weight ≤ 60 Kg, or serum creatinine ≥ 1.5 mg/dL/ t1/2=12 hrs	Hepatic CYP3A4/5/ Not needed	Thromboembolic stroke prevention in NVAF patients, DVT/ PE prevention in knee/hip replacement surgery, DVT/ PE treatment and recurrence prevention	Nausea	Non-Specific	Approved
	Rivaroxaban	Inhibits unbound and clot bound factor Xa	20 mg once daily (CrCl ≥ 50 mL/min) or 15 mg once daily (CrCl=30-49 mL/min)/ t1/2=5-9 hrs	CYP3A4/5 and CYP2J2/Not needed	DVT prophylaxis with hip/knee replacement surgery, stroke prevention in NVAF patients	Increased hepatic GGT	Non-specific	Approved
DTIs	Dabigatran etixilate	Inhibits clot formation by binding to thrombin active site	150 mg twice daily (CrCl > 30 mL/ min) or 75 mg twice daily (CrCl=15-30 mL/min)/ t1/2=12-17 hrs	Renal metabolism with the remaining becomes glucuronic acid conjugates in the liver/Not needed	Stroke prevention in patients with NVAF, Primary prevention of VTE in patients have undergone elective total hip/ knee arthroplasty	Dyspepsia	Idarucizumab undergoing clinical studies	Approved

Note: NVAF: Non-Valvular Atrial Fibrillation; PE: Pulmonary Embolism; VTE: Venous Thromboembolism; CrCl: Creatinine Clearance and GGT: Y-Glutamyl Transpeptidase

METHODOLOGY

Phase III RCTs that mentioned warfarin as the major comparator to each challenging NOVAC and showed analysis of stroke reduction and safety outcomes in patients with AF were chosen for this review. Other studies discussing the use of novel anticoagulants in different conditions other than AF were excluded. All data associated with the primary efficacy/safety outcomes as well as other outcomes along with data concerning drug-related side effects were collected from three major phase III RCTs (the RE-LY, the ROCKET-AF and the ARISTOTLE) addressing the comparison between warfarin and the NOVACs dabigatran, rivaroxaban and apixaban, respectively, in preventing AF-associated stroke. These selected RCTs reporting accomplished data were selected to directly address patient categories who are at risk of developing stroke due to AF. Elucidations about important pharmacologic properties, including monitoring requirements of the mentioned drugs, are included in this review as well.

RESULTS AND DISCUSSION

Three major phase III RCTs: Randomized Evaluation of Long-term anticoagulant therapY (RE-LY), 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) and Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) investigating dabigatran, rivaroxaban and apixaban as NOVACs, respectively, were identified [34-38]. A summary of the data illustrating the three RCTs comparing warfarin to NOVACS regarding the effectiveness and safety of preventing stroke in patients with AF is conducted in Table 2.

Table 2: The three major phase III RCTs on NOVACs in relation to patients with AF.

RCT name	RE-LY [8,35,36]			ROCKET AF [8,37]			ARISTOTLE [8,38]
Warfarin *vs.* NOVAC	**Warfarin**	**Dabigatran 150 mg**	**Dabigatran 110 mg**	**Warfarin**	**Rivaroxaban**	**Warfarin**	**Apixaban**
Study characteristics	N=18,113 AF patients Mean age=71 years Mean CHADS2 score=2.1			N=14,264 AF patients Mean age=73 years Mean CHADS2=3.5			N=18,201 AF patients Mean age=70 years Mean CHADS2=2.1
	Assigned groups: Warfarin (2-3; INR), or twice daily: Dabigatran 150 mg, or Dabigatran 110 mg twice daily			Assigned groups: Warfarin (2-3; INR), or Rivaroxaban 20 mg, or Rivaroxaban 15 mg (CrCl*=30-49 mL/min) once daily			Assigned groups: Warfarin (2-3; INR), or twice daily: Apixaban 5 mg, or Apixaban 2.5 mg**
Stroke or systemic embolism[i]	1.69%	1.11% P<0.001	1.53% P<0.001	2.40%	2.10% P<0.001	1.60%	1.27% P<0.001
Major bleeding[ii]	3.36%	3.11% P=0.31	2.71% P=0.003	3.40%	3.60% P=0.58	3.09%	2.13% P<0.001
Intracranial bleeding[ii]	0.74%	0.30% P<0.001	0.23% P<0.001	0.70%	0.50% P=0.02	0.80%	0.33% P<0.001
Death from any cause	4.13%	3.64% P=0.051	3.75% P=0.013	4.90%	4.50% P=0.15	3.94%	3.52% P=0.047
Conclusion	150 mg dabigatran dose was superior to warfarin and 110 mg dabigatran dose was non-inferior to warfarin for the primary efficacy endpoint. 110 mg dabigatran dose lowered the rate of major bleeding compared to warfarin. This rate was similar between 150 mg dabigatran dose and warfarin.			Differences between warfarin and rivaroxaban for the primary efficacy and safety endpoints did not reach statistical significance.			Apixaban was superior to warfarin for the primary efficacy and safety endpoints.

*Creatinine clearance, **Patients who met 2 or more of the following criteria: age ≥ 80, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL were assigned to 2.5 mg apixaban twice daily, [i]Stroke or systemic embolism is the primary efficacy endpoint, [ii]Major bleeding and intracranial bleeding are the primary safety endpoints.

RCTS WORKFLOW

Studies design

The RE-LY trial is a randomized, open-label and blinded endpoint clinical trial. In this trial, 18,113 AF patients were assigned to either 150 mg (high) or 110 mg (low) twice daily doses of blinded dabigatran or (2-3) INR-adjusted warfarin doses (1 mg, 3 mg, or 5 mg) that were unblended. With a median of 2 years of follow-up, their therapeutic suitability was ascertained by measuring the INR on a monthly basis. The ROCKET-AF and the ARISTOTLE are randomized, double-blind and double-dummy clinical trials that involved 14,264 and 18,201 patients, respectively. During a median of 1.9 years of follow-up, the ROCKET-AF patients were assigned to either rivaroxaban as 20 mg once daily (15 mg for creatinine clearance (CrCl) of 30-49 mL/min) or an INR (2-3) adjusted warfarin dose. In the ARISTOTLE, patients were assigned to 2.5 mg apixaban twice daily if ≥ 2 of the following criteria: age ≥ 80, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL were applicable. Otherwise, 5 mg twice daily doses of apixaban were used. Warfarin was given as 2 mg on the basis of (2-3) INR-adjusted doses and the non-naïve warfarin patients were entitled to discontinue treatment three days prior to randomization, with resuming this control drug after confirming < 2 INR was achieved. Results from this study were achieved after 1.8 years of follow-up [37,38].

Inclusion/Exclusion criteria

Patients in the RE-LY trial were considered eligible if they had an Electrocardiograph (ECG) documented AF at their enrolment. Otherwise, patients who had AF within the previous 6 months were also eligible if at least one of the following was present: previous stroke or transient ischemic attack (TIA), 40% Left Ventricular Ejection Fraction (LVEF), Heart Failure (HF) of New York Heart Association (NYHA) class II or higher within 6 months prior to screening, age ≥ 75 years, or an age of 65-74 years with Diabetes Mellitus (DM), hypertension, or coronary artery disease. Excluded patients were those with stroke of 14 days' duration prior to screening, severe stroke within the previous 6 months, severe heart valve disease and disease with suspected high haemorrhagic risk, CrCl of 30 mL/min, pregnancy and active liver disease [34].

In the ROCKET-AF, the enrolled AF patients were assessed to have at least moderate risk of stroke by having a minimum CHADS2 score of 2 with prior stroke or TIA. Or, at least 2 of the other CHADS2 risk factors (hypertension, DM, HF, or LVEF of ≤ 35% and age of ≥ 75 years). Excluded patients were those with severe stroke, severe mitral stenosis and history of intracranial bleeding, active bleeding and transient AF due to a reversible cause.

Included patients in the ARISTOTLE were known with AF or atrial flutter at the enrolment, with ECG records showing ≥ 2 episodes of AF two weeks apart within one year before enrollment. Also, one of the following CHADS2 risk factors was a requirement: age ≥ 75, history of previous stroke, TIA, symptomatic HF within the past 3 months, LVEF ≤ 40%, DM and hypertension under treatment control. Patients with a reversible cause of AF, moderate to severe mitral stenosis, conditions needed anticoagulation rather than AF (e.g., prosthetic heart valves), stroke within the last week prior to enrolment, aspirin use of > 165 mg/day and severe renal impairment (serum creatinine >2.5 mg/dL or CrCl < 25 mL/min) were excluded [35].

Characteristics of the enrolled patients

In the RE-LY trial, patients' characteristics included a mean age of 71 years, 64% median Time in Therapeutic Range (TTR) for the INR-adjusted warfarin, a mean CHADS2 score of 2.1, 20% history of previous stroke or TIA, the use of warfarin by 50% of the participants prior to enrollment and an average blood pressure of 131/77 mm Hg. In the ROCKET-AF trial, characteristics of the enrolled participants involved a 73-year median age, a 55% median TTR, an assessed median CHADS2 score of 3.5 and eligibility by having an ECG-documented AF with a moderate to severe risk of stroke, while others with potential bleeding risk were excluded. The ARISTOTLE study included a minimal of one CHADS2 risk factor of stroke, patients with a mean age of 70 years, a mean CHADS2 score of 2.1 and 62% TTR [8,35,36].

STATISTICAL ANALYSIS

Intention to Treat (ITT) analysis

To avoid major complications such as non-compliance and missing outcomes in the RCTs, ITT-analysis was used. This involved the inclusion of all the patients who were randomized in the RCTs. It was used to eliminate non-compliance, withdrawal, protocol deviations, as well as anything that occurred after randomization. This helped in maintaining a prognostic balance that was generated from the random treatment allocations [39].

Hazard Ratio (HR) and Relative Risk (RR)

By definition, RR is simply the accumulated hazard risk over the entire period of the clinical trial, while HR represents the same type of risk, but only over a specific period within the trial. The hazard risk refers to the number of patients excluded from the study compared to the expected number. This number should be estimated at the beginning of the study in the case of the RR or at the beginning of a specific period within the study in the case of the HR. This risk should always be taken into consideration when designing clinical trials. This importance came from the fact that it is impossible to know if this hazard was caused by the treatment itself or just randomly happened. Thus, both the HR and the RR affect the results of clinical trials differently and unexpectedly if ignored. When calculated, they present important differences in the effect of treatment, which may be obscured, especially when the proportions of recovered patients within the treatment group are compared to those of the control group at a particular point in time [40].

The non-inferiority or superiority

In all of the trials, a small sample of patients was used at the beginning to prove that NOVAC treatments are, at least not less effective than warfarin. This evidence of non-inferiority was used to extend the size of the trials, aiming to prove the superiority of the NOVACs use. All of the trials were designed taking into consideration the RR values. Those values were estimated from the accumulated data of all of the previous studies. In all of the trials, the upper bound of the one-sided CI's for the RR of each NOVAC's treatment compared to warfarin was needed to fall below 1.46. For this purpose, 95%, 97.5% and a 99% CI were used with the ROCKET-AF, the RE-LY and the ARISTOTLE trials, respectively. In all of the trials, the NOVACs treatment was considered non-inferior to warfarin when the one-sided P-values were less than 0.025. On the other hand, and in the case of proving superiority, the NOVACs were considered more effective than warfarin when the two-sided P-values were less than 0.05 [35-38].

RCTS ENDPOINTS

Comparison for the primary efficacy endpoint

The primary efficacy endpoint was related to the rate of stroke or systemic embolism among all of the RCTs [35]. The net beneficial effect of both dabigatran doses is believed to be associated with the remarkably improved effectiveness in the prevention of stroke in patients with AF [24,41]. When given in a low dose, dabigatran resulted in similar effectiveness to warfarin in the prevention of stroke and systemic embolism in the setting of AF. When it was given as a high dose, dabigatran significantly resulted in more favorable therapeutic efficacy than warfarin, while it seemed to be associated with similar rates of major bleeding to warfarin [42]. In the RE-LY trial, both dabigatran doses were non-inferior to warfarin ($P < 0.001$). Results of low dose dabigatran for the primary efficacy endpoint showed 1.53%/year (RR, 0.91; 95% CI, 0.74 to 1.11; $P=0.34$ and $P < 0.001$ for non-inferior testing) and 1.69%/year for warfarin. While for the high dose of dabigatran, the rate was less at 1.11%/year (RR, 0.66; 95% CI, 0.53 to 0.82; $P < 0.001$ for superiority testing). In total, a significant reduction by 34% was related to dabigatran high dose, while a 9% reduction among the similarity to warfarin was related to dabigatran low dose for stroke or systemic embolism [8,35].

In the ROCKET-AF, rivaroxaban was not inferior to warfarin with regard to the rate of stroke and systemic embolism (2.1%/year with rivaroxaban *vs.* 2.4%/year with warfarin, HR, 0.88, 95% CI, 0.74 to 1.03; P <0.001 for non-inferior testing) [8,37]. In the ARISTOTLE, the annualized rate for the primary efficacy outcome was 1.27% with apixaban and 1.60% with warfarin (HR with apixaban, 0.79; 95% CI, 0.66 to 0.95; P=0.001 for superiority testing). The risk of stroke or systemic embolism was significantly reduced with apixaban by 21% [38]. Also, in subgroup analyses, apixaban was favorable compared with warfarin independent of baseline stroke risk (CHADS2 of 1, 2 or ≥ 3) and history of stroke or TIA [43].

Comparison for the primary safety endpoint

A haemorrhagic stroke occurrence was included with the primary safety outcomes of all three trials. In the RE-LY, the annualized rate of haemorrhagic stroke was 0.38%, 0.12% and 0.1% with warfarin, dabigatran low dose (RR, 0.31; 95% CI, 0.17 to 0.56; P <0.001) and dabigatran high dose (RR, 0.26; 95% CI, 0.14 to 0.49; P <0.001), respectively [35,44,45]. In the ARISTOTLE, the annualized rate of haemorrhagic stroke was reported as 0.24% with apixaban *versus* 0.47% with warfarin treatment groups (HR, 0.51; 95% CI, 0.35 to 0.75; P <0.001) [38,46]. Both dabigatran doses were similar for the rate of haemorrhagic stroke and haemorrhagic stroke was less with apixaban by 49% compared to warfarin [35,38].

Major haemorrhage and intracranial bleeding were related to the other primary safety endpoints of the trials [8,16]. Both of the dabigatran doses produced less intracranial bleeding than warfarin. The low dabigatran dose proved a better safety endpoint than warfarin with fewer occurrences of major bleeding, where it also reduced the rate of hospitalizations. Similar major bleeding rates to warfarin were produced by dabigatran high dose (3.36%/year *vs.* 3.11%/year, RR, 0.93, 95% CI, 0.81-1.07; P=0.31, respectively) [35,36]. While preserving a similar efficacy to warfarin for stroke and systemic embolism prevention, the low dabigatran dose proved a superior beneficial outcome by significantly reducing the rate of major bleeding (2.71%/year, RR, 0.80, 95% CI, 0.69-0.93; P=0.003) in comparison to warfarin. In addition, both doses reduced intracranial bleeding *versus* warfarin treatment (0.30%/year with dabigatran high dose, RR, 0.26, 95% CI, 0.14-0.49; P=0.001 *vs.* 0.23%/year with dabigatran low dose, RR, 0.31, 95% CI, 0.17-0.56; P=0.001 *vs.* 0.74%/year with warfarin) [8,33,35]. In the ARISTOTLE, the annualized rate of major bleeding was 2.13% with apixaban and 3.09% with warfarin (HR, 0.69, 95% CI, 0.60 to 0.80; P <0.001). A significant reduction in major bleeding by 31% was associated with apixaban. The rate of intracranial bleeding was 0.33%/year with the apixaban group, while it was associated with 0.80% in the warfarin group (HR, 0.42; 95% CI, 0.30 to 0.58; P <0.001). Therefore, apixaban was considered to be superior to warfarin with less intracranial bleeding while resulting in fewer overall bleeding events and a lower discontinuation rate than warfarin [33,38].

The ROCKET-AF is described as a non-inferiority trial. The safety considerations were investigated as a possible advantage that could be offered by the use of rivaroxaban in this trial. The associated major and non-major clinically significant bleeding were the main safety measures of interest. Similar major bleeding events of 3.6%/year and 3.4%/year were noticed between rivaroxaban and warfarin in the ROCKET-AF (HR, 1.04, 95% CI, 0.90-1.20; P=0.58), respectively. Clinically relevant major and non-major bleeding was similarly associated between the rivaroxaban treatment group (14.9%/year) and warfarin group (14.5%/year) (HR, 1.03; 95% CI, 0.96 to 1.11; P=0.44). Intracranial haemorrhage occurred as 0.5%/year and 0.7%/year (HR, 0.67, 95% CI, 0.47-0.93; P=0.02) with rivaroxaban and warfarin, respectively. This explains that intracranial bleeding was significantly lower with rivaroxaban than warfarin. In addition, bleeding associated with critical anatomical sites or proved fatal was lower with rivaroxaban than warfarin (0.2%/year *vs.* 0.5%/year; P=0.003). This was explained mainly by lower rates of haemorrhagic stroke, intracranial haemorrhage, bleeding mortality and critical organ bleeding with rivaroxaban than warfarin. Furthermore, data associated with the ROCKET-AF sub-analysis proved that rivaroxaban had a consistent efficacy and safety across a wide range of patients. However, as there was no significant difference in the rates of major and non-major bleeding between the treatments, this led the investigators to conclude with the non-inferiority of rivaroxaban through the ITT analysis [8,37,47,48].

Summary: Among the overall primary efficacy and safety endpoints, apixaban represents the combined favorable effects of dabigatran in high and low doses. Apixaban was superior to warfarin in overall outcomes. Apixaban in a dose of 5 mg twice daily not only can reduce the rate of stroke but also can result in a lower bleeding rate than warfarin [8,50].

Further analysis of the primary efficacy and safety endpoints

The NOVACs' non-inferior results could have been impacted by the differences in the CHADS2 risk score and TTR of the enrolled patients in all trials. The greatest CHADS2 risk score was amongst the ROCKET-AF patients (mean CHADS2 score=3.5), as compared to the RE-LY (mean CHADS2 score=2.1) or the ARISTOTLE (mean CHADS2 score=2.1). The primary efficacy outcome in the RE-LY showed that high-dose dabigatran was superior to warfarin. However, beyond the mean CHADS2 score, the subgroup analysis (CHADS2 score ≥ 3) showed that high-dose dabigatran did not result in superiority but rather showed a non-inferior trend to warfarin. Similarly, this could be a contributing factor that may have affected the comparison between the ROCKET-AF and the ARISTOTLE. On the other hand, TTR was 55% with the ROCKET-AF and was lower than the TTRs of the other trials (62% with the ARISTOTLE and 64% with the RE-LY). Among the patients outside the TTR (45 % in the ROCKET-AF), two thirds were classified with the sub-therapeutic INR (<2). Consequently, this is another factor that broadens the difference in stroke risk between the major trials. Thereby, this may explain why the efficacy results among rivaroxaban treatments were similar to those of warfarin. The detected differences in stroke risk were reflected in the non-inferiority results in the ROCKET-AF [8,33,51].

There were three important findings from the ARISTOTLE, which demonstrated superior benefits of apixaban over the other NOVAC's that were investigated through the RE-LY and the ROCKET-AF. First of all, results from the ARISTOTLE showed a consistent efficacy of apixaban over warfarin in terms of reducing stroke or systemic embolism, major hemorrhage and overall mortality, regardless the type of AF. Furthermore, the consistency of apixaban among those efficacy and safety measures was produced consistently and irrespective of the duration of AF, it lasted from the first documented AF until randomization. Lastly, the risk of stroke or systemic embolism in addition to major hemorrhage or overall mortality was higher with the persistent rather than paroxysmal-AF.

Despite all differences among the baseline characteristics and the outcomes associated with each AF type, apixaban was consistent in producing a superiority over warfarin regarding all of the safety and efficacy outcomes [49].

Other outcomes/side effects

Mortality: In the RE-LY trial, the annualized mortality rate from any cause were 4.13%, 3.75% and 3.64% with warfarin, dabigatran low dose (RR, 0.91, 95% CI, 0.80-1.03; P=0.13) and dabigatran high dose (RR, 0.88, 95% CI, 0.77-1.00; P=0.051), respectively [35]. In the ARISTOTLE trial, the associated annual rate of death from any cause was 3.52% with apixaban and 3.94% in relation to warfarin-treatment group (HR, 0.89, 95% CI, 0.80-0.99; P=0.047). Apixaban was better in reducing death by 11% than warfarin [38,50]. Through the ITT-analysis, the annualized rate of death was similar in ROCKET-AF between both of the treatments (4.5%/year with rivaroxaban and 4.9%/year with warfarin, HR, 0.92, 95% CI, 0.82-1.03; P=0.15) [37]. Overall, NOVACs have a trend to reduce the mortality risk when compared to warfarin [16].

Cardiovascular events: The RE-LY trial showed statistically higher Myocardial Infarction (MI) rates with both dabigatran doses than warfarin. MI rates were 0.82%/year (RR, 1.29; 95% CI, 0.96-1.75) with dabigatran low dose and 0.81% (RR, 1.27, 95% CI, 0.94-1.71) with dabigatran high dose (0.81%/year for both dabigatran doses), while the rate of this endpoint was 0.64%/year with warfarin. This may demonstrate better protection against the ischemic coronary events with warfarin than dabigatran and warfarin is known to reduce the risk of MI. The pathogenesis of this is unclear, where it could be attributed to the undesirable effect of dabigatran, favorable coronary protection with warfarin, or the play of chance with dabigatran; however, the magnitude of dabigatran beneficial outcomes in terms of stroke reduction provided better outcomes in comparison to this effect [23,33,35,51]. In the ROCKET-AF, MI occurred at a rate of 0.9%/year with rivaroxaban and as 1.1%/year with warfarin (HR with rivaroxaban, 0.81, 95% CI, 0.63-1.06; P=0.12) [37]. The ROCKET-AF showed no significant differences between rivaroxaban and warfarin in lowering MI and the mortality rate [51]. Apixaban reduced the rate of MI in comparison to warfarin through the ARISTOTLE trial, while the difference was insignificant between the treatment groups for this outcome (0.53% *vs.* 0.61%, HR, 0.88, 95% CI, 0.66-1.17; P=0.37, respectively). Also, the rate of MI was lower with apixaban in comparison to aspirin through the Apixaban *versus* Acetylsalicylic acid (ASA) to Prevent Strokes (AVERROES) trial [51-53]. Results of apixaban lowering the rate of MI in the ARISTOTLE trial presented a more favorable secondary outcome than the other NOVACs [16,51].

Gastrointestinal side effects: Dabigatran-associated dyspepsia was significantly higher with both dabigatran doses (11.8% and 11.3% with low and high doses; P=0.001, respectively) than warfarin (5.8%) [13,35]. This side effect led to about 21% of dabigatran discontinuation [23]. This more frequent discontinuation in dabigatran treatment was as a result of GI distress and a high level of active drug in the colon, suggesting that dabigatran may not be an ideal choice for patients with a history of GI distress [54].

Despite the lower overall rates of major bleeding with dabigatran, GI bleeding was increased with dabigatran high dose (1.56%/year) in comparison to warfarin (1.07%/year, RR, 1.48, 95% CI, 1.18-1.85) and dabigatran low dose (1.15%/year, RR; 1.36, 95% CI, 1.09-1.70). In clinical practice, dabigatran was reported to have a potential risk of life-threatening GI bleeding. Fatal rectal bleeding has been indicated as a case report. Since dabigatran absorption is enhanced in the presence of low pH, the formulation of dabigatran capsules consists of dabigatran-coated pellets with a core of tartaric acid. This may form a part of the impact that increased the dyspeptic effect of both dabigatran doses and increased the GI bleeding risk with dabigatran high dose [35,52,55].

In the ROCKET-AF, GI bleeding rate was higher in the rivaroxaban group as compared to the warfarin group (3.2% *vs.* 2.2%; P <0.001), respectively. This involved upper, lower and rectal sites. This bleeding was associated with a drop in the hemoglobin level, or blood transfusion [37]. In contrast, apixaban resulted in reduced or comparable rates of GI bleeding to warfarin (0.76% with apixaban *vs.* 0.86% with warfarin, HR, 0.89, 95% CI, 0.7-1.15; P=0.37) in the ARISTOTLE trial [51,52].

Summary: Among all of these newer agents, apixaban improved all of the primary efficacy and safety outcomes. The risk of overall mortality, MI and the rate of GI bleeding in clinical practice were all lower with apixaban in comparison to warfarin.

NOVACs dosing and monitoring requirements

Anticoagulation preferences: Unlike warfarin, dabigatran, rivaroxaban and apixaban have pharmacokinetic behavior that is consistent and enables giving them in a fixed dose. The fixed dosage of NOVACs does not require monitoring and adjustments to present desirable effects. Also, they have a selective inhibitory mechanism towards thrombin or factor Xa, while warfarin, which is difficult to control, inhibits a broad array of pro- and anti-coagulant factors (factors II, VII, IX and X and proteins C and S). Subsequently, NOVACs have a lower risk of haemorrhage [33,35,53].

CYP450/P-glycoprotein, renal function and dose adjustment: The excretion of both rivaroxaban and dabigatran is highly dependent on renal function. Therefore, dosage adjustment is required for both of these agents with renal impairment. While only 25% of apixaban excretion is renal, this implies to its safer usage in patients with severe renal impairment. However, the administration of this drug necessitates cautious monitoring in patients with hepatobiliary disease. In addition, warfarin will be used as a standard choice in patients with CrCl 30 mL/min. Avoidance of CYP450 is a characteristic associated with dabigatran, while all of these newer agents are efflux substrates of P-glycoprotein (P-gp), as they may interact with P-gp inhibitors or inducers. On the other hand, apixaban and rivaroxaban are metabolized by CYP3A4 and they are subject to drug interactions. This does not indicate any superiority of warfarin, as its metabolism with CYP450 exhibits a wide range of variability. Consequently, the administration of these drugs is more convenient [33,52,56].

Warfarin

Warfarin is predominantly metabolized by the highly polymorphic CYP2C9 *via* an oxidation process. Two common variant alleles of CYP2C9 gene (CYP2C9*2 and CYP2C9*3) are associated with reduced enzymatic activity. One copy of any of the CYP2C9 variant alleles is associated with reduced warfarin metabolism and lower rates of clearance. The carriers of these alleles are more likely to receive lower warfarin doses and they seem to be at a higher risk of bleeding complications as it takes longer for the warfarin therapy to be adjusted on the therapeutic INR. Metronidazole, trimethoprim/sulfamethoxazole and amiodarone are examples of the commonly

prescribed drugs with an inhibitory effect on CYP2C9. When co-administered with warfarin, these drugs produce a significant effect on the INR and bleeding risk [57,58].

Dabigatran, rivaroxaban and apixaban

The concomitant use of P-gp and CYP3A4 inducers such as phenytoin and carbamazepine should be avoided, as they are more likely to decrease dabigatran, rivaroxaban and apixaban efficacy. P-gp inhibitors such as verapamil, ketoconazole and amiodarone are associated with increased serum levels of dabigatran; however, according to the US FDA, this increase seems to be clinically insignificant and does not necessitate dabigatran dose reduction. Azole antimycotics or Human Immunodeficiency Virus (HIV) protease inhibitors are strong inhibitors of CYP3A4 and P-gp. Therefore, rivaroxaban and apixaban are not recommended in patients receiving these drugs, while apixaban's dose could be adjusted to 2.5 mg twice daily. However, for certain less potent inhibitors (e.g., diltiazem), the US FDA labeling shows no precautions when they are coadministered with rivaroxaban, while they could be coadministered with apixaban.

Dabigatran dose adjustment or the use of an alternative anticoagulant is recommended in patients with moderately impaired renal function (CrCl of 15-50 mL/min) and on the concurrent use of P-gp inhibitors. With severe renal impairment of CrCl ranging between 15 mL/min to 30 mL/min, the European health system recommends against the use of dabigatran; however, in the US, dabigatran dose can be adjusted to 75 mg once daily for AF-associated stroke prevention. Regardless of renal function status, the Health Canada labeling recommends against the concurrent use of dabigatran and a strong P-gp inhibitor. For patients with CrCl of 15-30 mL/min, rivaroxaban may be coadministered with mild to moderate CYP3A4 inhibitors when benefits outweigh the risks. In addition, in the presence of two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg and serum creatinine ≥ 1.5 mg/dL, the coadministration of apixaban with these potent CYP3A4 and P-gp inhibitors is avoided [32,34,59,60].

Regarding all of the CYP3A4 and P-gp inducers or inhibitors, their effects can either increase or decrease exposure to NOVACs to varying degrees depending on the interacting drug. For example, ketoconazole represents the strongest inhibitory interaction that increases exposure to dabigatran and rivaroxaban by 150%-160%, while the strong inducer rifampicin causes at least a 50% reduction of the exposure to NOVACs. Therefore, both of the strong inducers or inhibitors of CYP3A4 and P-gp are avoided in terms of concomitant use with NOVACs. The majority of these drugs also interact with warfarin, but with the accessibility to the INR level measures among warfarin treatment, the dose can be adjusted to mitigate any expected risk from concomitant use [55].

CONCLUSION

Despite the long history supporting the use of vitamin K antagonists, their effectiveness in thromboembolic event prevention has been hampered by several limitations. In contrast to warfarin, no clinical trials mention the need for coagulation monitoring with fixed-dose NOVACs. NOVACs may conduct an alternative choice to warfarin in patients who are unwilling to have frequent blood tests and for whom maximized therapeutic efficacy cannot be attained using warfarin. In reference to data from the main three RCTs (Table 2), NOVACs have demonstrated comparable or more desirable outcomes over the standard vitamin K antagonist warfarin for the primary efficacy and safety endpoints. These data were obtained from studies conducted on patients with AF and were mostly known to have a moderate to severe risk of developing thromboembolic events. However, these data were only presented from limited phase III clinical trials that encompassed variations in patients' characteristics and strict inclusion/exclusion criteria. Therefore, additional data from phase IV RCTs actively incorporating warfarin should assess whether NOVACs will account for an appropriate alternative regarding their efficacy and safety in preventing AF-associated stroke.

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