Comparative effectiveness of rivaroxaban in the treatment of nonvalvular atrial fibrillation

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Rivaroxaban is a direct oral anticoagulant (DOAC) approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, a common arrhythmia. In this review, we summarize the effectiveness of rivaroxaban versus warfarin and the DOACs dabigatran, apixaban and edoxaban. The primary focus is on primary evidence from clinical trials, indirect comparison studies and real-world studies. While there are gaps in the literature, the evidence thus far indicates that rivaroxaban is superior to warfarin and similar to dabigatran, apixaban and edoxaban for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation, although rivaroxaban may be associated with an elevated bleeding risk compared with other DOACs.

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Overview

Rivaroxaban is a direct oral anticoagulant (DOAC) approved by the US FDA on 4 November 2011 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAf). Rivaroxaban has also been approved for the treatment of venous thromboembolism and the prophylaxis of deep venous thrombosis (DVT) following hip or knee replacement surgery, but that will not be the focus of this review. Patients with any type of NVAf, whether permanent, persistent or paroxysmal, and whether they are symptomatic or asymptomatic, are at increased risk of thromboembolic ischemic stroke [1–4], with NVAf patients experiencing fivefold higher rates of stroke than those without NVAf [1]. For patients with diagnosed NVAf, the current ACC/AHA/HRS Guideline for the Management of Patients with AF recommends oral anticoagulation in those with a prior stroke

or transient ischemic attack, or those with a moderate or greater risk of stroke (CHA₂DS₂-VASc score ≥1 in males or ≥2 in females) [5]. Vitamin K antagonist anticoagulants, with warfarin being the most common, have been historically prescribed. However, with the recent advent of DOACs including rivaroxaban, dabigatran, apixaban and edoxaban, these new anticoagulants have now become commonly used.

This review article provides an overview of the comparative effectiveness of rivaroxaban in the treatment of NVAf for the prevention of stroke and systemic embolism. The focus of this manuscript is on key, defining developments rather than providing a comprehensive literature survey. First, we briefly outline the pharmacology of rivaroxaban, and second we review the evidence from the Phase III clinical trial, including sub-analyses, and summarize indirect comparison studies between DOACs. Third, we review

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the comparative evidence from real-world studies. We end by highlighting special populations and potential areas for additional research. To inform the review, we searched PubMed through 15 March 2017 using the broad search terms ‘rivaroxaban’ and ‘nonvalvular atrial fibrillation’ or ‘nonvalvular atrial fibrillation’, focusing on existing meta-analyses if they were available. Case reports were not considered. Though related to the topic, we do not review rivaroxaban effectiveness when given concurrently to patients undergoing cardioversion, or administered before or during procedures, such as percutaneous coronary intervention.

Pharmacology

Rivaroxaban is a direct Factor Xa inhibitor that inhibits both free Factor Xa and Factor Xa bound in the prothrombinase complex [6]. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and the development of thrombi. Rivaroxaban does not require routine monitoring or dose adjustments, and there are no known dietary restrictions, therefore allowing for predictable anticoagulation. For patients with NVAF, rivaroxaban is administered as a single daily dose of 20 mg for most patients or 15 mg for those with reduced kidney function. When used to treat DVT or pulmonary embolism, patients are prescribed a dose of 15 mg twice daily for the first 21 days, and then transitioned to a once-daily 20 mg dose for the remaining treatment. A 20-mg dose is prescribed to reduce the risk of recurrent DVT and pulmonary embolism. A dosing of once-daily, 10 mg is recommended for prophylaxis of DVT following hip or knee replacement surgery [7]. Peak plasma time is 2–4 h, with a half-life of 5–9 h in healthy patients aged 20–45, and 11–13 h in elderly patients [8]. Rivaroxaban for the treatment of NVAF is usually administered in a once a day dose (recommended to be taken with the evening meal), leading to higher compliance and persistence versus warfarin [9–11]. A summary of relevant characteristics for rivaroxaban is listed in Table 1 [7,8].

Clinical trial

In the large Phase III double-blind randomized controlled trial ROCKET-AF (Rivaroxaban once daily oral direct factor Xa inhibitor compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation), 14,264 NVAF patients at moderate-to-high risk of stroke were randomized to receive a once-daily fixed dose of rivaroxaban or adjusted-dose warfarin. Those randomized to rivaroxaban experienced lower rates of intracranial hemorrhage, critical bleeding and fatal bleeding than those assigned to warfarin [12]. Risk of the primary end point, stroke or

systemic embolism, was 12% lower in patients assigned to rivaroxaban compared with those assigned to warfarin (intention-to-treat hazard ratio [HR], 95% confidence interval [CI]: 0.88 [0.75; 1.03]), which was not statistically significant versus warfarin ($p < 0.001$ for noninferiority, $p = 0.12$ for superiority). However, rivaroxaban users were at increased risk for major bleeding from a gastrointestinal (GI) site, compared with warfarin users (HR: 1.42 [95% CI: 1.22; 1.66]) [13]. Rates of secondary efficacy outcomes, including myocardial infarction (MI), and all-cause mortality did not differ significantly between groups. Estimates for the main outcomes from ROCKET-AF are summarized in Table 2. Additionally, rivaroxaban users were more likely to experience epistaxis and hematuria compared with warfarin users while other adverse events did not differ significantly between groups [12].

Post-trial, concerns were raised regarding therapeutic international normalized ratio measures in the warfarin (control) arm of the clinical trial data [14,15]. However, posthoc analysis indicates randomized patients were equally distributed among the recalled international normalized ratio measuring device, and re-analysis accounting for the possible malfunction of the point-of-care device indicates results consistent with the overall trial findings [15].

A few subgroup analysis of the ROCKET-AF trial should be mentioned. The treatment effect of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism was consistent regardless of the time in therapeutic range in warfarin users [16]. Elderly patients had higher stroke and major bleeding rates compared with younger patients, but the efficacy and safety of rivaroxaban compared with warfarin did not differ with age [17]. Patients with renal impairment (creatinine clearance 30–49 ml/min) experienced higher rates of stroke and bleeding compared with patients with normal renal function, but the rates did not differ between warfarin and the reduced dose of rivaroxaban (15 mg) [18]. The treatment effect of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism was comparable regardless of diabetes status [19], heart failure [20] and previous stroke [21]. Lastly, in comparing efficacy and risks separately in vitamin K antagonist-naïve and vitamin K antagonist-experienced patients, rivaroxaban was associated with a similar risk of ischemic stroke as warfarin users in both groups, and a decreased risk of bleeding versus warfarin only in the vitamin K antagonist-naïve group [22].

Indirect comparisons with other DOACs

Overview

In addition to rivaroxaban, there are currently three other DOACs (dabigatran, apixaban and edoxaban)

Table 1. Main descriptive characteristics for rivaroxaban for the treatment of patients with nonvalvular atrial fibrillation.

Summary	Rivaroxaban
Recommended dose	20 mg once per day (with food)
Alternative dose	15 mg if creatinine clearance is 15–49 ml/min
Time to maximum plasma concentration	2–4 h
Half-life	5–9 h (young); 11–13 h (elderly)
Excretion	2/3 liver, 1/3 renal
Contraindications or patient groups for which use is not recommended	Creatinine clearance <15 ml/min; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk (including Child-Pugh B and C); age <18 years; pregnancy or breast feeding; hypersensitivity to the active substance or excipients
Use with caution (close monitoring for bleeding/anemia)	Creatinine clearance 15–29 ml/min, patients with an increased bleeding risk (e.g., congenital or acquired bleeding disorders; uncontrolled severe arterial hypertension; active ulcerative GI disease; recent GI ulcerations; vascular retinopathy; recent intracranial or intracerebral hemorrhage; intraspinal or intracerebral vascular abnormalities; recent brain, spinal or ophthalmic surgery; bronchiectasis or history of pulmonary bleeding)
Warnings	Because of an increased risk of thrombotic events, consider administering another anticoagulant if rivaroxaban needs to be discontinued for any reason other than pathological bleeding

GI: Gastrointestinal.

that have been approved by the FDA for the prevention of stroke and systemic embolism in NVAf patients. In brief, all of the DOACs have shorter half-lives and take less time to reach maximum blood concentration compared with warfarin. Unlike warfarin, DOACs have a specific target (either thrombin or factor Xa), do not require routine coagulation monitoring and can be administered with fixed doses.

The DOACs

Dabigatran, a direct thrombin inhibitor, was the first DOAC to be FDA approved (October 2010), and is a fixed twice-daily dose of either 110 or 150 mg. Data from the Phase III clinical trial, the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, showed both doses were noninferior or superior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism [23]. Additional studies indicate dabigatran is associated with a lower risk of stroke and intracranial bleeds compared with warfarin, however, dabigatran users may be more at risk of GI bleeds and MI compared with warfarin users [23–25].

Next, apixaban is an oral direct factor Xa inhibitor, and was FDA approved in December 2012. Apixaban has a rapid onset (1–4 h) and short elimination half-life

(12 h), and is dosed twice daily, at a dose of 5 mg, with a reduced dose of 2.5 mg recommended in certain patients, such as those age ≥80 years with a specific comorbidity. In the Phase III ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) clinical trial, apixaban was superior to warfarin in preventing stroke or systemic embolism, and additionally caused less bleeding and resulted in lower mortality when compared with warfarin [26].

Finally, edoxaban is a factor Xa inhibitor, and was FDA approved in January 2015. In the Phase III clinical trial, ENGAGE-AF-TIMI (Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48), patients were randomized to either a 60- or 30-mg dose. Results from the trial indicate both doses of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism, and were associated with significantly lower rates of bleeding and cardiovascular death [27]. The rate of stroke was lower with high-dose edoxaban than with low dose, although the rates for bleeding (major bleeding, intracranial bleeding and major/clinically relevant nonmajor bleeding) were lower in the low-dose edoxaban compared with the high-dose [27]. Edoxaban has a high renal clearance

Table 2. Hazard ratios (95% confidence intervals) for the association of rivaroxaban with the comparator drug for main outcomes in patients with nonvalvular atrial fibrillation.

Rivaroxaban vs:	Clinical trial	Real-world data		
	ROCKET-AF [12,13]	Real-world data meta-analysis [46]		Claims database [48]
	Warfarin	Warfarin	Dabigatran	Apixaban
Stroke or systemic embolism	0.88 (0.75; 1.03)	0.75 (0.64; 0.85) [†]	1.02 (0.91; 1.13)	0.95 (0.58; 1.56)
Ischemic stroke	0.91 (0.73; 1.13)	0.86 (0.75; 0.97) [†]	0.98 (0.88; 1.08)	0.79 (0.45; 1.38)
Intracranial bleeding	0.67 (0.47; 0.93) [†]	0.54 (0.43; 0.64) [†]	1.22 (0.85; 1.59)	1.79 (0.68; 4.69)
Major bleeding	1.03 (0.90; 1.18)	0.99 (0.91; 1.07)	1.38 (1.27; 1.49) [†]	2.56 (1.85; 3.56) [†]
Gastrointestinal bleeding	1.42 (1.22; 1.66) [†]	1.20 (1.07; 1.33) [†]	1.33 (1.18; 1.48) [†]	N/A
Any bleeding	N/A	1.01 (0.94; 1.08)	1.33 (1.17; 1.49) [†]	N/A
Myocardial infarction	0.81 (0.63; 1.06)	0.73 (0.30; 1.15)	0.81 (0.43; 1.29)	N/A
All-cause mortality	0.85 (0.70; 1.02)	1.04 (0.64; 1.44)	1.23 (1.12; 1.33) [†]	N/A

Estimates are hazard ratio (95% confidence interval).
[†]Statistically significant results.
 N/A: Not available.

rate, and therefore, should not be prescribed in patients with creatinine clearance >95 ml/min [27,28]. Due to the relatively new approval date of edoxaban, limited data exist on the comparative effectiveness between edoxaban and rivaroxaban at this time, but we will briefly mention published data on pooled clinical trial data and indirect comparisons.

Pooled clinical trial results & indirect comparisons

Several meta-analyses were performed using pooled data from the clinical trials involving rivaroxaban, dabigatran and apixaban, and a few more recent analyses add in edoxaban. Overall, compared with warfarin, patients randomized to any of the DOACs had a 19% lower risk of stroke or systemic embolism (HR: 0.81 [95% CI: 0.73; 0.91]) [29] and significant reductions in intracranial bleeding, total mortality and cardiovascular disease (CVD) mortality [29–32]. Most studies reported no difference with major bleeding and GI bleeding between warfarin versus the DOACs [30–34]; however, one study reported increased GI bleeding in DOAC users compared with warfarin (HR: 1.25 [95% CI: 1.01; 1.55]) [29].

Several indirect comparison studies of DOACs using data from each of the Phase III clinical trials were conducted, and are summarized in Table 3. When accessing the relative effect of the different treatment options in each study, patients receiving full-dose dabigatran had a 26% lower risk of stroke and systemic embolism

compared with those receiving rivaroxaban [35]. When the odds of major or clinically relevant bleeding in each study were compared with each other, the risk was 34% lower in apixaban compared with rivaroxaban, and additionally, more MI events were seen in dabigatran (>50%) compared with rivaroxaban [35,36]. There were no significant differences between high-dose edoxaban versus rivaroxaban for efficacy end points or mortality, but rivaroxaban had more major/clinically relevant nonmajor bleeding [37]. Specifically, among patients with a CHADS₂ score ≥2, rivaroxaban users had a higher risk of major bleeding compared with high-dose edoxaban [38]. These indirect comparisons provide important information; however, these results should be interpreted with caution because of differences in study designs and patient populations between the Phase III trials [32,39]. For example, the participants enrolled in the ROCKET-AF trial had a higher prevalence of comorbidities, including a higher risk for stroke (CHADS₂ score of 3.5) versus the clinical trials for the other three drugs.

Real-world rivaroxaban safety & effectiveness, post clinical trial Rivaroxaban versus warfarin

Several real-world, population-based studies have conducted post clinical trial on the safety and effectiveness of rivaroxaban versus warfarin, which generally confirm the findings of the trial and show similar results even in unselected populations [40].

Table 3. Summary of the indirect comparison results for rivaroxaban versus the other direct oral anticoagulants in patients with nonvalvular atrial fibrillation.

Study		Ref.
Lip <i>et al.</i>:		[35]
– Source population	The three randomized clinical trials: RE-LY, ROCKET-AF, ARISTOTLE	
– Significant findings	Rivaroxaban users had a higher risk of stroke and systemic embolism compared with dabigatran 150-mg users. Major bleeding risk higher in rivaroxaban vs apixaban. Compared with dabigatran 110-mg users, rivaroxaban users had more major bleeding and intracranial bleeding	
– Methods	Assess relative effect of treatment interventions using a common comparator (warfarin), through the Bucher method	
– Limitations	The three clinical trials enrolled populations that differed, and also employed different study designs. Notably, ROCKET-AF patients were slightly older, were at higher stroke risk (means CHADS2 score 3.5), and 55% were a secondary prevention population	
Mantha & Ansell		[36]
	Similar finding as the Lip <i>et al.</i> study. The methods differed in that Mantha and Ansell used indirect comparison techniques based on the odds ratios of an event for patients receiving one drug vs the other	
Skjoth <i>et al.</i>:		[37]
– Source population:	Four randomized clinical trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE-AF	
– Significant findings:	No differences between high-dose edoxaban vs rivaroxaban for efficacy end points or mortality, but rivaroxaban users had more major and/or clinically relevant nonmajor bleeding. Versus low dose edoxaban, rivaroxaban was associated with lower risk of stroke/systemic embolism and ischemic stroke, but higher bleeding rates	
– Methods	Same as the Lip <i>et al.</i> paper	
– Limitations	Similar limitations as mentioned above. The ENGAGE-AF population had an intermediate stroke risk compared with the other trials	
Fernandez <i>et al.</i>:		[38]
– Source population	Phase III trials (n = 4); Phase II and Phase III trials with warfarin (n = 15); Subgroup analysis of Phase III trials of RE-LY, ROCKET-AF, ARISTOTLE (n = 14)	
– Significant findings	High dose edoxaban was associated with lower major bleeding compared with rivaroxaban. Risk of stroke and systemic embolism was similar. Low dose edoxaban was associated with a lower risk of major bleeding than rivaroxaban	
– Methods	Network meta-analysis using methods to minimize potential biases resulting from differences in patient clinical characteristics between the trials and from differences in the duration of study follow-up	
– Limitations	Despite methods to control differences, unmeasured confounders still exist. For example, no information on concomitant aspirin dosage is available in two of the clinical trials	

XANTUS (Xarelto on preveNtion of sTroke and noncentral nervoUS system) was the first large, prospective, single-arm, observational Phase IV study of rivaroxaban for stroke prevention in NVAF. The results from this study were similar to the Phase III clinical trial, with a favorable risk-benefit profile for rivaroxaban versus warfarin [41]. Data from anticoagulation registries and large claims or electronic

databases provide similar results: for nonrandomized NVAF patients in the real-world, rivaroxaban was associated with either a lower or similar risk for the prevention of stroke or systemic embolism compared with patients taking warfarin [9,11,41–44], and was also associated with a high treatment adherence [11,45]. A recent meta-analysis of real-world studies quantifies the association: the annual stroke or systolic

embolism rate was lower in rivaroxaban patients versus warfarin patients (HR: 0.75 [95% CI: 0.64; 0.85]) including a reduction in the risk of ischemic stroke (HR: 0.86 [95% CI: 0.75; 0.97]) [46]. Main outcomes from this meta-analysis are summarized in Table 2. Regarding safety outcomes, compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality and MI, but a higher risk of GI bleeding (HR: 1.20 [95% CI: 1.07; 1.33]) and lower risk of intracranial bleeding (HR: 0.54 [95% CI: 0.43; 0.64]) [46]. A recent study using registry data showed similar risk of ischemic stroke/systemic embolism in patients with NVAf receiving the reduced dose of rivaroxaban (15 mg) compared with warfarin users [47].

Direct comparisons between DOACs

No clinical trials have been conducted randomizing patients to the different DOACs; however, head-to-head comparisons on the effectiveness of the drugs have been performed in large, real-life datasets. Table 2 summarizes the major outcomes from direct comparison studies. A recent meta-analysis concluded dabigatran and rivaroxaban have a similar risk of stroke or systemic embolism (HR: 1.02 [95% CI: 0.91; 1.13]) but major bleeding is 38% higher in rivaroxaban versus dabigatran [46]. Additionally, GI bleeding risk (HR: 1.33 [95% CI: 1.18; 1.48]) and all-cause mortality (HR: 1.23 [95% CI: 1.12; 1.33]) were higher in rivaroxaban versus dabigatran [46]. A study using US claims data from Optum Labs Data Warehouse included 57,788 DOAC users with NVAf and concluded rivaroxaban, dabigatran and apixaban have similar effectiveness in preventing stroke or systemic embolism, although apixaban was associated with a lower bleeding risk versus rivaroxaban (HR: 0.39 [95% CI: 0.28; 0.54]) and rivaroxaban was associated with an increased risk of major bleeding (HR: 1.30 [95% CI: 1.10; 1.53]) and intracranial bleeding (HR: 1.79 [95% CI: 1.12; 2.86]) compared with dabigatran [48]. Finally, in another US commercial-claims based study, this one using data from the MarketScan healthcare claims database that was limited to 45,361 anticoagulant-naïve users, rivaroxaban initiation was associated with a higher risk of major bleeding compared with apixaban initiation (HR: 1.82 [95% CI: 1.36; 2.43]) [42]. In summary, in large healthcare claims databases, the results have been fairly consistent: Dabigatran, rivaroxaban and apixaban appear to have similar effectiveness in the prevention of stroke or systemic embolism in patients with NVAf, although rivaroxaban is associated with an elevated bleeding risk, while apixaban may be associated with the lowest bleeding risk.

Special populations

Elderly

A few studies have explored associations in the upper age-range in the elderly, but this area needs additional research. In elderly Medicare patients, head-to-head comparisons of the effectiveness of dabigatran versus rivaroxaban indicate similar stroke rate, but rivaroxaban initiators had an increased risk of intracranial bleeding and major bleeding, including GI bleeds [49]. A Danish study found supporting results in a nationwide registry, although in this study, rivaroxaban users were older with more comorbidities compared with dabigatran users. The rivaroxaban users had similar stroke rates compared with dabigatran users, but higher bleeding and mortality. The authors concluded that routing of rivaroxaban toward elderly and less healthy patients may have generated residual confounding [50], explaining the associations with bleeding and mortality.

Asian

The J-ROCKET AF Phase III clinical trial was conducted in Japan comparing a Japan-specific reduced dose of rivaroxaban (15 mg once daily or 10 mg in those with low creatinine clearance) to a warfarin dose adjusted according to Japanese guidelines. Rivaroxaban was noninferior to warfarin for the outcome of stroke or systemic embolism, and rivaroxaban significantly decreased the incidence of ischemic stroke (HR: 0.40 [95% CI: 0.17; 0.96]) compared with warfarin [51]. Intracranial bleeding rates were 0.8% with rivaroxaban and 1.6% with warfarin. In addition, rivaroxaban users had decreased incidence of GI bleeding compared with warfarin users [51]. Edoxaban has also performed well in Japanese studies, and based on these results, the following recommendations regarding the selection of DOACs are suggested for Japanese patients: edoxaban for patients with a high risk of bleeding and those with a previous stroke; rivaroxaban for patients with a high risk of ischemic stroke and a low bleeding risk, and those with previous GI bleeding [52]. Small studies, yet noteworthy results, indicate that for Chinese [53,54] and East Asian patients [55], rivaroxaban is associated with lower stroke and intracranial bleeding rates compared with warfarin.

Liver injury

Isolated cases of liver injury associated with rivaroxaban use have been published [56]. Rivaroxaban experiences some hepatobiliary metabolism, and hepatic impairment could alter the drug's effect on anticoagulation. Available data suggest rivaroxaban can be used in patients with mild hepatic impairment [57], but should be avoided in patients with severe liver

impairment, such patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients classified as Child-Pugh B and C [58]. A study of 113,717 patients with NVAf using the MarketScan healthcare claims database assessed the risk of hospitalization with liver injury after initiation of oral anticoagulation. The study found rivaroxaban initiators had similar risk of liver injury compared with warfarin users. However, compared with dabigatran initiators, rivaroxaban initiators had a 56% increased risk of liver injury hospitalization (HR: 1.56 [95% CI: 1.22; 1.99]) [59]. This association should be more thoroughly explored in additional studies.

The issue of GI bleeding

Overall, there is a consistent, elevated risk of bleeding, particularly GI bleeding, in rivaroxaban patients compared with warfarin, dabigatran and apixaban users. There appears to be an increased risk in the elderly, those with a higher CHA₂DS₂-VASc score and those age >75 years [49,50,60,61]. There are currently risk scores for the assessment of bleeding risk, including the often-used HAS-BLED score [62]. However, these scores have been developed for the prediction of bleeding among NVAf patients using warfarin, and future research should develop bleeding risk scores specifically for patients on DOACs [63]. Factors independently associated with major bleeding in DOAC studies included increased age, male, higher diastolic blood pressure, prior GI bleeding, prior acetylsalicylic acid use and anemia [44,64]. Further studies should examine and expand on these patient characteristics to be able to identify in advance individuals most at risk of rivaroxaban-associated GI bleeding events.

Gaps in knowledge

Differences by sex

Despite a lower prevalence of NVAf in women than in men, women generally experience worse quality of life and have a higher risk of stroke and death when compared with men [65]. In NVAf patients treated with warfarin, women have a significantly greater risk of stroke and systemic embolism than their male counterparts [66]. Among patients treated with DOACs, one study found there was no difference by sex in risk of stroke, however women treated with DOACs may have less major bleeding than men [67]. An indirect comparison study using data from the clinical trials found there was no difference in safety or efficacy for women [68]. An important consideration is that the clinical trials were not powered to study sex differences in anticoagulant use. Studies using large, real-world datasets for head-to-head comparisons of

DOACs should consider stratifying by sex or reporting sex-specific results. Additionally, reporting sex-specific risks of other bleeding events such as epistaxis, hematuria and menorrhagia would be of interest. Several small studies have reported higher rates of menorrhagia in women with venous thromboembolism taking rivaroxaban [69–71], and although the patient population with NVAf tends to be older, these are areas of interest, and could warrant a reason for prescribing one DOAC versus another.

New users versus switchers

It is of clinical importance to assess whether switching from warfarin to rivaroxaban is associated with adverse outcomes compared with anticoagulant-naïve rivaroxaban initiators. Previous studies have reported inconsistent results in outcomes when switching from warfarin to a DOAC [25,72]. ROCKET-AF contained both types of patients, and in subgroup analysis, found the efficacy was similar in both groups but there was a decreased risk of ischemic stroke in the vitamin K antagonist-naïve initiators [22]. Subsequent real-world studies have contained a mix of new users, switchers and unclassified patients. A meta-analysis indicated rivaroxaban new users showed superior effectiveness to warfarin for ischemic stroke and stroke/systemic embolism prevention, but switchers showed similar risks [46]. Additionally, the clinical trial indicated an increased risk in first 7 days after switching from warfarin to rivaroxaban, but after 30 days, rivaroxaban users had similar bleeding compared with switchers [22]. In the clinical trial, as well as real-life studies, an increased risk of bleeding in switchers could be confounded by clinical factors that make patients switch from warfarin to a DOAC, such as an adverse reaction to or complication from using warfarin, or the patient's inability to stabilize his/her warfarin dose. However, there may still be benefits of switching from warfarin to a DOAC, and the benefits appear to be independent of time-in-therapeutic range under warfarin [73]. In XANTUS, the Phase IV trial, results indicate switching from warfarin to rivaroxaban yielded improvements in anticlot treatment scores and benefit scores [74]. Future real-world studies should examine the effectiveness of rivaroxaban in anticoagulant-naïve or experienced users, and also the timing of adverse outcomes in relation to switching to rivaroxaban.

New stroke prevention approaches in patients with NVAf

Cardioembolic stroke is a major complication of patients with NVAf, and while oral anticoagulation has reduced the risk of ischemic stroke, there are patient populations

that are not eligible or not ideal candidates for anticoagulation. In 2015, a mechanical left atrial appendage occlusion device (the Watchman) was approved for stroke prevention in patients with NVAF [75,76]. Recently, a network meta-analysis was performed between the randomized clinical trials of the DOACs and the Watchman device. Indirect comparisons between rivaroxaban and the Watchman device resulted in a similar risk for stroke or systemic embolism (HR: 1.20 [95% CI: 0.23; 6.34]) in those with the Watchman versus rivaroxaban [77]. As more real-life data become available, better comparisons for the effectiveness of the Watchman versus rivaroxaban or additionally, the Watchman in conjunction with rivaroxaban, should be conducted.

Patients with prevalent conditions

Patients with malignancies may have an increased risk of bleeding, depending on the cancer type and state, along with renal and liver function and the presence thrombocytopenia. Additionally, patients on chemotherapy could be at increased bleeding risk. Data on the use of rivaroxaban for stroke prevention in cancer patients with NVAF are lacking, and would be of interest to clinicians considering NVAF patients may be at an increased risk for cancer [78].

Questions remain regarding the use of anticoagulation in those with prior events such as GI bleeding, intracranial bleeding, stroke, patients with reduced kidney function, severe anemia or thrombocytopenia. Additionally, if a patient has one of these events or a bleeding event while on anticoagulation, the question of whether to continue anticoagulation, and if so, the timing of anticoagulation re-initiation following the event is currently a clinically relevant question.

Drug interactions with rivaroxaban

Anticoagulation properties of the DOACs are more predictable and stable (i.e., less influenced by interactions with foods, supplements, prescribed drugs and over-the-counter medications) when compared with warfarin. However, data on pharmacodynamic interactions and drug interactions with foods, herbal supplements, prescribed drugs and over-the-counter medications are sparse, particularly for real-world data. A recent review paper states that in rivaroxaban users, concomitant treatment with strong inhibitors of both CYP3A4 and P-gp is contraindicated. No significant effects have been reported when aspirin, naproxen or clopidogrel were co-administered with rivaroxaban, although clopidogrel did prolong the mean bleeding time [79]. Additionally, the co-administration of rivaroxaban with other anticoagulant drugs is discouraged due to the additive effect. Additional food, drug and supplement interactions with rivaroxaban may be an area for future exploration.

Antidote

In the USA, numerous lawsuits have been filed against Janssen Pharmaceutical and Bayer Healthcare (the manufacturer and marketer of rivaroxaban) by patients who have suffered severe bleeding as a result of taking the medication. Currently, there is no reversal agent for Factor Xa inhibitors, which include rivaroxaban, apixaban and edoxaban. In 2015, Portola Pharmaceuticals published results from a Phase III clinical trial using their antidote for rivaroxaban, andexanet alfa (AndexXa) [80]. However, in 2016, the FDA delayed approval of the biologics license, although small clinical trials show promising data for the antidote [81]. For the time being, before an antidote becomes available, there are existing strategies for management of major bleeding associated with Factor Xa inhibitors [82].

Conclusion

While there are gaps in the literature, the evidence thus far consistently indicates that rivaroxaban is superior to warfarin and similar to dabigatran and apixaban for the prevention of stroke and systemic embolism in patients with NVAF, although rivaroxaban may be associated with an elevated bleeding risk, particularly GI bleeding, compared with warfarin and other DOACs.

Future perspective

The incidence and prevalence of NVAF are expected to increase with the aging of the population, increasing the burden from its associated complications, such as stroke. Current risk scores for stroke prediction provide modest support for treatment decisions involving anticoagulation. We foresee stroke risk/benefit stratification schemes will continue to evolve and assist clinicians and patients in treatment decisions, including developing predictive models for bleeding events and other adverse effects for the DOACs. Long-term effects of the DOACs will be quantified, and safety in special populations will be accessed. Antidotes for Factor Xa inhibitors including rivaroxaban will be approved, and additional alternatives to DOACs, such as the Watchman and similar devices, will be compared with DOACs for the prevention of stroke in NVAF patients. Then end result will likely be an individual-specific risk/benefit profile for the potential effectiveness of each of the treatments for patients with NVAF.

Disclaimer

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The

Summary points**Overview**

- Rivaroxaban is a direct oral anticoagulant (DOAC) approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), a common arrhythmia.
- In this review, we give a brief overview of rivaroxaban and then compare the effectiveness of rivaroxaban versus warfarin and the other new DOACs including dabigatran, apixaban and edoxaban.

Pharmacology

- Rivaroxaban is a direct factor Xa inhibitor that does not require routine monitoring or dose adjustments, thereby allowing for predictable anticoagulation.
- The drug is administered as a single daily dose of 20 mg for most patients with NVAF, while a 15 mg dose is recommended for those with reduced renal function (creatinine clearance 15–49 ml/min).

Clinical trial

- The Phase III clinical trial, ROCKET-AF, reported patients randomized to rivaroxaban experienced nonsignificant lower rates of stroke or systemic embolism, and lower rates of intracranial hemorrhage, critical bleeding and fatal bleeding compared with warfarin users.
- Rivaroxaban users experienced an increased risk for gastrointestinal bleeding compared with warfarin users.

Indirect comparisons of DOACs

- Patients receiving any of the DOACs had a lower risk of stroke or systemic embolism, and significant reductions in intracranial bleeding, total mortality and cardiovascular mortality compared with warfarin users.

Real-world rivaroxaban safety & effectiveness, postclinical trial

- Rivaroxaban has similar effectiveness as dabigatran and apixaban for the prevention of stroke and systemic embolism in patients with NVAF.
- Rivaroxaban may be associated with an elevated bleeding risk compared with other oral anticoagulants.

Special populations

- The risk of bleeding is higher in elderly patients and those with a higher CHA₂DS₂-VASc score, and the use of rivaroxaban in these patients may exacerbate the bleeding risk.
- A reduced dose of rivaroxaban in Japanese patients decreases the risk of stroke and bleeding versus warfarin use.
- Rivaroxaban users may be at increased risk of liver injury versus dabigatran users.

Gaps in knowledge

- There is more research to be conducted to determine the effectiveness of rivaroxaban in real-world patients.
- Areas for growth include sex differences, switching to rivaroxaban from another anticoagulant, comparisons with new methods for stroke prevention, use in patients with comorbidities and drug interactions.

Conclusion

- The evidence consistently indicates the effectiveness of rivaroxaban is superior to warfarin and similar to dabigatran and apixaban for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- Rivaroxaban use is associated with an elevated bleeding risk, most commonly gastrointestinal bleeding, in most populations.

author maintained full control over the manuscript, including content, wording and conclusions.

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