Review

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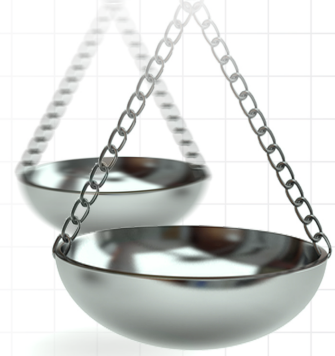

Journal of **Comparative Effectiveness Research**

Comparative effectiveness of rivaroxaban in the treatment of nonvalvular atrial fibrillation

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 (CHA_2DS_2-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-analyzes, 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-analyzes 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-naive 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-naive 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 $CHADS_2$ 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 *et al.*:		[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	Similar finding as the Lip *et al.* 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	[36]
Skjoth *et al.*:		[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 *et al.* paper	
– Limitations	Similar limitations as mentioned above. The ENGAGE-AF population had an intermediate stroke risk compared with the other trials	
Fernandez *et al.*:		[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-naive 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 CHA_2DS_2-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-naive 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-naive 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-naive 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 CHA_2DS_2-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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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 22(8), 983–988 (1991).

2 Glotzer TV, Daoud EG, Wyse DG *et al.* The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ. Arrhythmia Electrophysiol.* 2(5), 474–480 (2009).

3 Ziegler PD, Glotzer TV, Daoud EG *et al.* Detection of previously undiagnosed atrial fibrillation in patients with

stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. *Am. J. Cardiol.* 110(9), 1309–1314 (2012).

4 Ziegler PD, Glotzer TV, Daoud EG *et al.* Incidence of newly detected atrial arrhythmias via implantable devices in patients with a history of thromboembolic events. *Stroke* 41(2), 256–260 (2010).

5 January CT, Wann LS, Alpert JS *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 130(23), e199–e267 (2014).

6 Roehrig S, Straub A, Pohlmann J *et al.* Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59–7939): an oral, direct factor Xa inhibitor. *J. Med. Chem.* 48(19), 5900–5908 (2005).

7 Janssen Pharmaceuticals Inc. Xarelto® (rivaroxaban) Prescribing Information (2013). https://www.xarelto-us.com

8 Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin. Pharmacokinet.* 53(1), 1–16 (2014).

9 Laliberte F, Cloutier M, Nelson WW *et al.* Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr. Med. Res. Opin.* 30(7), 1317–1325 (2014).

10 Nelson WW, Song X, Coleman CI *et al.* Medication persistence and discontinuation of rivaroxaban versus warfarin among patients with non-valvular atrial fibrillation. *Curr. Med. Res. Opin.* 30(12), 2461–2469 (2014).

11 Beyer-Westendorf J, Camm AJ, Coleman CI, Tamayo S. Rivaroxaban real-world evidence: validating safety and effectiveness in clinical practice. *Thromb. Haemost.* 116(Suppl. 2), S13–S23 (2016).

12 Patel MR, Mahaffey KW, Garg J *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New Engl. J. Med.* 365(10), 883–891 (2011).

•• **The ROCKET-AF trial.**

13 Sherwood MW, Nessel CC, Hellkamp AS *et al.* Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial. *J. Am. Col. Cardiol.* 66(21), 2271–2281 (2015).

14 Cohen D. Rivaroxaban: can we trust the evidence? *BMJ* 352, i575 (2016).

15 Patel MR, Hellkamp AS, Fox KA. Point-of-care warfarin monitoring in the ROCKET AF trial. *New Engl. J. Med.* 374(8), 785–788 (2016).

16 Piccini JP, Hellkamp AS, Lokhnygina Y *et al.* Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. *J. Am. Heart Assoc.* 3(2), e000521 (2014).

17 Halperin JL, Hankey GJ, Wojdyla DM *et al.* Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in 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). *Circulation* 130(2), 138–146 (2014).

18 Fox KA, Piccini JP, Wojdyla D *et al.* Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur. Heart J.* 32(19), 2387–2394 (2011).

19 Bansilal S, Bloomgarden Z, Halperin JL *et al.* Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: 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). *Am. Heart J.* 170(4), 675.e8–682.e8 (2015).

20 Van Diepen S, Hellkamp AS, Patel MR *et al.* Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ. Heart Failure* 6(4), 740–747 (2013).

21 Hankey GJ, Patel MR, Stevens SR *et al.* Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol.* 11(4), 315–322 (2012).

22 Mahaffey KW, Wojdyla D, Hankey GJ *et al.* Clinical outcomes with rivaroxaban in patients transitioned from vitamin K antagonist therapy: a subgroup analysis of a randomized trial. *Ann. Intern. Med.* 158(12), 861–868 (2013).

23 Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl. J. Med.* 361(12), 1139–1151 (2009).

24 Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 145(1), 105e.15–112.e15 (2013).

25 Bengtson LG, Lutsey PL, Chen LY, MacLehose RF, Alonso A. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J. Cardiol.* 69(6), 868–876 (2017).

26 Granger CB, Alexander JH, Mcmurray JJ *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *New Engl. J. Med.* 365(11), 981–992 (2011).

27 Giugliano RP, Ruff CT, Braunwald E *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *New Engl. J. Med.* 369(22), 2093–2104 (2013).

28 Bohula EA, Giugliano RP, Ruff CT *et al.* Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 134(1), 24–36 (2016).

29 Ruff CT, Giugliano RP, Braunwald E *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 383(9921), 955–962 (2014).

• **A meta-analysis of the Phase III trials.**

30 Dogliotti A, Paolasso E, Giugliano RP. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large,

randomized, controlled trials vs warfarin. *Clin. Cardiol.* 36(2), 61–67 (2013).

31 Jia B, Lynn HS, Rong F, Zhang W. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. *J. Cardiovasc. Pharmacol.* 64(4), 368–374 (2014).

32 Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. *Thrombosis* 2013, 640723 (2013).

33 Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation* 126(20), 2381–2391 (2012).

34 Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am. J. Cardiol.* 110(3), 453–460 (2012).

35 Lip GY, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J. Am. Col. Cardiol.* 60(8), 738–746 (2012).

36 Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. *Thromb. Haemost.* 108(3), 476–484 (2012).

37 Skjoth F, Larsen TB, Rasmussen LH, Lip GY. Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. An indirect comparison analysis. *Thromb. Haemost.* 111(5), 981–988 (2014).

38 Fernandez MM, Wang J, Ye X *et al.* Systematic review and network meta-analysis of the relative efficacy and safety of edoxaban versus other nonvitamin K antagonist oral anticoagulants among patients with nonvalvular atrial fibrillation and CHADS2 score 2. *SAGE Open Med.* 3, 2050312115613350 (2015).

39 Marietta M. Direct oral anticoagulants in atrial fibrillation: can data from randomized clinical trials be safely transferred to the general population? No. *Intern. Emerg. Med.* 10(6), 647–650 (2015).

40 Riva N, Ageno W. Direct oral anticoagulants in atrial fibrillation: can data from randomized clinical trials be safely transferred to the general population? Yes. *Intern. Emerg. Med.* 10(6), 641–645 (2015).

41 Camm AJ, Amarenco P, Haas S *et al.* XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur. Heart J.* 37(14), 1145–1153 (2016).

• **Summarized the results of XANTUS.**

42 Lip GY, Keshishian A, Kamble S *et al.* Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb. Haemost.* 116(5), 975–968 (2016).

• **A propensity-score matched real-world comparison study.**

43 Coleman CI, Antz M, Ehlken B, Evers T. REal-LIfe Evidence of stroke prevention in patients with atrial fibrillation - The RELIEF study. *Intern. J. Cardiol.* 203, 882–884 (2015).

44 Tamayo S, Frank Peacock W, Patel M *et al.* Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. *Clin. Cardiol.* 38(2), 63–68 (2015).

45 Russo V, Rago A, Proietti R *et al.* Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: the real-life evidence. *Ther. Adv. Drug Safety* 8(2), 67–75 (2017).

46 Bai Y, Deng H, Shantsila A, Lip GY. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation: systematic review and meta-analysis. *Stroke* 48(4), 970–976 (2017).

•• **The recent meta-analysis by Bai *et al.***

47 Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 356, j510 (2017).

48 Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, Mcbane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *Chest* 150(6), 1302–1312 (2016).

•• **The direct comparison study by Noseworthy *et al.***

49 Graham DJ, Reichman ME, Wernecke M *et al.* Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern. Med.* 176(11), 1662–1671 (2016).

50 Gorst-Rasmussen A, Lip GY, Bjerregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. *Pharmacoepidemiol. Drug Saf.* 25(11), 1236–1244 (2016).

51 Hori M, Matsumoto M, Tanahashi N *et al.* Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. *Circulation J.* 76(9), 2104–2111 (2012).

52 Okumura K, Hori M, Tanahashi N, John Camm A. Special considerations for therapeutic choice of non-vitamin K antagonist oral anticoagulants for Japanese patients with nonvalvular atrial fibrillation. *Clin. Cardiol.* 40(2), 126–131 (2017).

53 Mao L, Li C, Li T, Yuan K. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in Chinese patients with atrial fibrillation. *Vascular* 22(4), 252–258 (2014).

54 Li WH, Huang D, Chiang CE *et al.* Efficacy and safety of dabigatran, rivaroxaban, and warfarin for stroke prevention in Chinese patients with atrial fibrillation: the Hong Kong Atrial Fibrillation Project. *Clinical Cardiol.* 40(4),222–229 (2017).

55 Wong KS, Hu DY, Oomman A *et al.* Rivaroxaban for stroke prevention in East Asian patients from the ROCKET AF trial. *Stroke* 45(6), 1739–1747 (2014).

56 Liakoni E, Ratz Bravo AE, Terracciano L, Heim M, Krahenbuhl S. Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. *JAMA Intern. Med.* 174(10), 1683–1686 (2014).

57 Kubitza D, Roth A, Becka M *et al.* Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br. J. Clin. Pharmacol.* 76(1), 89–98 (2013).

58 Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. *Clin. Pharmacokinet.* 52(4), 243–254 (2013).

59 Alonso A, Maclehose RF, Chen LY *et al.* Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. *Heart* 103(11), 834–839 (2017).

- **The paper by Alonso *et al.* regarding liver injury in direct oral anticoagulant users.**

60 Abraham NS, Singh S, Alexander GC *et al.* Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ* 350, h1857 (2015).

61 Peacock WF, Tamayo S, Patel M, Sicignano N, Hopf KP, Yuan Z. CHA2DS2-VASc scores and major bleeding in patients with nonvalvular atrial fibrillation who are receiving rivaroxaban. *Ann. Emerg. Med.* 69(5), 541–550 (2017).

62 Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1 year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138(5), 1093–1100 (2010).

63 Alonso A, Norby FL. Predicting atrial fibrillation and its complications. *Circulation J.* 80(5), 1061–1066 (2016).

64 Goodman SG, Wojdyla DM, Piccini JP *et al.* Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J. Am. Col. Cardiol.* 63(9), 891–900 (2014).

65 Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat. Rev. Cardiol.* 13(6), 321–332 (2016).

66 Ko D, Rahman F, Martins MA *et al.* Atrial fibrillation in women: treatment. *Nat. Rev. Cardiol.* 14(2), 113–124 (2017).

67 Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am. J. Cardiol.* 113(3), 485–490 (2014).

68 Moseley A, Doukky R, Williams KA, Jaffer AK, Volgman AS. Indirect comparison of novel oral anticoagulants in women with nonvalvular atrial fibrillation. *J. Womens Health (Larchmt)* 26(3), 214–221 (2017).

69 De Crem N, Peerlinck K, Vanassche T *et al.* Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared with vitamin K antagonists. *Thromb. Res.* 136(4), 749–753 (2015).

70 Ferreira M, Barsam S, Patel JP *et al.* Heavy menstrual bleeding on rivaroxaban. *Br. J. Haematol.* 173(2), 314–315 (2016).

71 Myers B, Webster A. Heavy menstrual bleeding on rivaroxaban – comparison with apixaban. *Br. J. Haematol.* 176(5), 833–835 (2017).

72 Bouillon K, Bertrand M, Maura G, Blotiere PO, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol.* 2(4), e150–e159 (2015).

73 Verdecchia P, Angeli F, Aita A, Bartolini C, Reboldi G. Why switch from warfarin to NOACs? *Intern. Emerg. Med.* 11(3), 289–293 (2016).

74 Coleman CI, Haas S, Turpie AG *et al.* Impact of switching from a vitamin K antagonist to rivaroxaban on satisfaction with anticoagulation therapy: the XANTUS-ACTS substudy. *Clin. Cardiol.* 39(10), 565–569 (2016).

75 Holmes DR Jr, Kar S, Price MJ *et al.* Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J. Am. Col. Cardiol.* 64(1), 1–12 (2014).

76 Holmes DR, Reddy VY, Turi ZG *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 374(9689), 534–542 (2009).

77 Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative effectiveness of interventions for stroke prevention in atrial fibrillation: a network meta-analysis. *J. Am. Heart Assoc.* 5(5), e003206 (2016).

78 Conen D, Wong JA, Sandhu RK *et al.* Risk of malignant cancer among women with new-onset atrial fibrillation. *JAMA Cardiol.* 1(4), 389–396 (2016).

79 Di Minno A, Frigerio B, Spadarella G *et al.* Old and new oral anticoagulants: food, herbal medicines and drug interactions. *Blood Rev.* doi:10.1016/j.blre.2017.02.001 (2017) (Epub ahead of print).

80 Siegal DM, Curnutte JT, Connolly SJ *et al.* Andexanet alfa for the reversal of factor Xa inhibitor activity. *N. Engl. J. Med.* 373(25), 2413–2424 (2015).

81 Connolly SJ, Milling TJ Jr., Eikelboom JW *et al.* Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N. Engl. J. Med.* 375(12), 1131–1141 (2016).

82 Christos S, Naples R. Anticoagulation reversal and treatment strategies in major bleeding: update 2016. *West. J. Emerg. Med.* 17(3), 264–270 (2016).