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REVIEW ARTICLE

Rivaroxaban in the Prevention of Stroke and Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation: Clinical Implications of the ROCKET AF Trial and Its Subanalyses

Ryan J. Spencer[1] · **John V. Amerena**[1]

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Abstract Atrial fibrillation (AF) is an increasingly common cause of stroke and systemic embolism. While warfarin has been the mainstay of stroke prevention in patients with AF, newer novel oral anticoagulant medications are now available. Rivaroxaban, a direct factor Xa inhibitor with a rapid onset and offset after oral administration, offers potential advantages over warfarin, predominantly due to its predictable pharmacokinetics across wide patient populations. It requires no coagulation monitoring, and only two different doses are needed (20 mg daily for patients with normal renal function and 15 mg daily in those with reduced renal function). A large randomized trial (ROCKET AF) has shown non-inferiority to warfarin for preventing stroke or systemic embolism in the per-protocol population and superiority to warfarin in the on-treatment safety population. Several subanalyses confirm that the treatment effect of rivaroxaban is consistent across different patient subgroups, including those with reduced renal function. The tolerability of rivaroxaban appears similar to that of warfarin, with comparable overall bleeding rates in clinical trials. In ROCKET AF, significantly lower rates of fatal and intracranial bleeding were seen with rivaroxaban, while lower rates of gastrointestinal bleeding were seen with warfarin. Important contraindications to rivaroxaban include valvular AF, the presence of a prosthetic valve (mechanical or bioprosthetic) or valve repair, the need for concurrent dual antiplatelet therapy, and creatinine clearance <30 ml/min. Once-daily dosing and the lack of coagulation monitoring may increase utilization and adherence compared with warfarin, potentially decreasing the large burden of care associated with stroke secondary to AF. Overall, rivaroxaban offers a useful alternative to warfarin for stroke prevention in patients with AF.

Key Points

Rivaroxaban is a new, oral-acting, direct factor Xa inhibitor that is currently available for stroke and systemic embolism prevention in patients with non-valvular AF.

A large randomized trial has shown efficacy equivalence with warfarin and lower rates of intracranial hemorrhage, with similar rates of bleeding overall.

Rivaroxaban can be used in patients with creatinine clearances down to 30 ml/min (with a dose reduction), but should be avoided in those with prosthetic valves, recent gastrointestinal bleeding and severe renal impairment.

1 Introduction

Atrial fibrillation (AF) is thought to account for 15–20 % of all ischemic strokes, and due to an increasingly aging population, is growing in prevalence. Studies predict that by the year 2050 there will be between 12 and 16 million patients with AF in the USA alone [1]. AF is associated with a four- to fivefold increased risk of ischemic stroke, this being its most devastating complication [2]. Of the

✉ John V. Amerena
johnamerena@gmail.com

[1] Deakin University, Geelong, VIC, Australia

800,000 strokes that occur each year in the USA, 1.5 % are attributable to AF in those aged under 59, while 23 % are attributable to AF in those aged over 80 [2]. Anticoagulation with the vitamin K antagonist warfarin has been the mainstay of stroke prevention in patients with AF. However, as treatment is complicated, involving frequent monitoring, adherence to a stable diet, and the possibility of serious side effects, newer anticoagulants have been developed. Rivaroxaban, a novel oral anticoagulant (NOAC) acting via an anti-factor Xa action, has emerged as one of four current alternatives to warfarin, and shall be the subject of this review.

While warfarin is effective at preventing ischemic stroke in patients with AF, it is plagued by underutilization, a narrow therapeutic window and rare but life-threatening bleeding complications. Studies of administrative databases reveal that 40–50 % of patients with AF, who are at substantial risk of stroke, are not taking appropriate anticoagulation [3, 4]. Even when warfarin is prescribed, rates of discontinuation range from 25–55 % over the first 2 years and, of those who continue, many spend large amounts of time outside the narrow therapeutic range [5, 6]. A US study, for example, recently revealed patients spend an average of 55 % of their time with a therapeutic international normalized ratio (INR) [7]. Unfortunately, when strokes do occur in patients with AF, they are more severe and are associated with higher 30-day and 1-year mortality when compared with strokes occurring in patients without AF [8].

Reasons for non-prescribing or discontinuation of warfarin include patient factors such as the need for intrusive regular monitoring and a constant diet, and patient/physician factors such as the fear of serious bleeding complications. Bleeding is warfarin's major side effect, with studies demonstrating an annual rate of major hemorrhage (intracranial bleeding or a bleed requiring hospitalization or 2 units of blood) of between 1 and 12 % [9, 10]. These factors suggest a large unmet need exists in stroke prevention among patients with AF, which newer oral anticoagulants may fill. Their ease of use (without the need for regular blood tests for monitoring), wider therapeutic window and lower rates of intracranial hemorrhage (the most feared complication of anticoagulation) may increase prescribing and continuation rates and thus contribute to lowering the large economic and social cost of stroke.

2 Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor with predictable pharmacokinetics and a rapid onset and offset after oral administration. It is predominately metabolized by the liver, via the CYP3A4 system, with approximately one-third excreted unchanged in the urine [11, 12]. Accordingly, concomitant use with the strong CYP3A4 inhibitors ketoconazole, itraconazole, lopinavir, ritonavir, and indinavir, or with the strong CYP3A4 inducers carbamazepine, phenytoin, rifampicin and St. John's wort is not recommended [13]. Renal excretion contributes to around one-third of the drug's metabolism, and thus higher serum levels are seen when a patient's creatinine clearance (CrCl) drops below 50 ml/3 min [14]. It is administered as a fixed dose without the need for coagulation monitoring and has a serum half-life of 5–9 h in young adults, 11–13 h in the elderly, and longer again in patients with renal dysfunction [15]. For this reason, strict compliance with daily dosing is critical, as missing one dose can result in a period without protection from thromboembolism.

Studies have demonstrated efficacy at preventing venous thromboembolism (VTE) after major, elective orthopedic surgery [16], in the treatment of acute VTE [17, 18], and in stroke prevention in patients with AF [19]. While no monitoring of drug levels or effect is required, a concentration-dependent prolongation of the prothrombin time (PT) does occur with rivaroxaban. Unfortunately, this is nonlinear and thus cannot be used to monitor the level of anticoagulation. The degree of prolongation also varies depending on the reagents used and cannot be standardized with the INR system commonly used for vitamin K antagonists [20]. The PT is therefore a useful way to assess for the presence of rivaroxaban in the circulation, but cannot be used to accurately measure the level of its effect.

3 Efficacy in Atrial Fibrillation

Rivaroxaban was studied in the context of stroke prevention in AF 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) trial [19]. This study randomized 14,264 AF patients at moderate to high risk of stroke (mean $CHADS_2$ score of 3.5) to either adjusted-dose warfarin targeting an INR of 2–3 or rivaroxaban 20 mg daily (or 15 mg daily in those patients with a CrCl of 30–49 ml/min). The study was a double-blind, double-dummy, event-driven trial conducted in 45 countries between December 2006 and May 2010. Key inclusion criteria included non-valvular AF, and either a $CHADS_2$ score of 2 or more, or a previous stroke, TIA or systemic embolism. Relevant exclusion criteria included left ventricular thrombus, planned cardioversion, prosthetic heart valve, blood pressure $\geq$180/100 mmHg, active internal bleeding, history of major surgical procedure or trauma within 30 days, gastrointestinal (GI) bleed within 6 months, history of intracranial bleeding or known

intracranial neoplasm, anemia (hemoglobin <100 g/l), any stroke within 14 days or TIA within 3 days, treatment with aspirin >100 mg/day or dual antiplatelet therapy (DAP), CrCl (as calculated by the Cockcroft Gault formula) <30 ml/min, or significant liver disease (e.g., cirrhosis or an ALT >3 times the upper limit of normal). The study population was representative of real-world AF patients, with an average age of 73, a slight majority of males (60 %) and frequent coexisting illnesses.

In the primary efficacy analysis, designed to test non-inferiority using the per-protocol population (those patients who received at least one dose of study medication, did not have a major protocol violation, and were followed while on treatment and for 2 days afterward), rivaroxaban was found to be non-inferior to warfarin for the composite primary endpoint of stroke (hemorrhagic or ischemic) and systemic embolism [1.7 % per year with rivaroxaban vs. 2.2 % per year with warfarin, hazard ratio (HR) 0.79; 95 % confidence interval (CI) 0.66–0.96; $P < 0.001$ for non-inferiority]. In the pre-specified superiority analysis, no difference was found in the intention-to-treat population. However, in a pre-specified analysis limited to the time patients were taking the study drug, rivaroxaban was superior to warfarin for the above composite primary endpoint (1.7 % per year with rivaroxaban vs. 2.2 % per year with warfarin, HR 0.79; 95 % CI 0.65–0.95; $P = 0.01$ for superiority). This difference reflects the dilutional effect of the 23 % of patients who discontinued the study drug (both warfarin and rivaroxaban), as no difference in stroke rates was observed after discontinuation.

Bleeding rates between the two drugs were no different overall, although warfarin had higher rates of intracranial hemorrhage and rivaroxaban had higher rates of GI bleeding. No difference was found in rates of other, non-bleeding-related, adverse events amongst the two groups. A number of subgroup analyses have shown similar efficacy and safety amongst patients with previous stroke or TIA [21], peripheral artery disease [22], heart failure [23], those undergoing cardioversion or AF ablation [24], and those previously treated with warfarin [25].

4 Important Considerations

Relevant contraindications to rivaroxaban therapy in AF include significant renal impairment (CrCl < 30 ml/min), the presence of a prosthetic heart valve (bioprosthetic or mechanical), valvular AF, coexisting need for DAP, history of intracranial hemorrhage, or recent GI bleed. In ROCKET AF, increased rates of GI bleeding were seen with rivaroxaban compared with warfarin, suggesting warfarin may be safer in patients at high risk of this complication. Conversely, lower rates of intracranial hemorrhage were seen with rivaroxaban, suggesting that it could be considered in patients with a past history of intracranial hemorrhage, although this has not been formally evaluated. Anticoagulation decisions in this group of patients are challenging, and options include off-label use of rivaroxaban or one of the other NOACs, or percutaneous left atrial appendage closure (which alleviates the need for any anticoagulation) [26].

No trials evaluating the efficacy of rivaroxaban in patients with mechanical prosthetic heart valves have been performed. However, the one study to examine the use of NOACs in these patients showed dabigatran was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin [27]. Therefore, at this time, patients with AF and a prosthetic heart valve (and AF caused by significant valvular disease) require warfarin for anticoagulation. Similarly, no trial evaluating the safety of the AF doses (20 or 15 mg) of rivaroxaban with concurrent DAP therapy has occurred, thus, making this combination experimental at this stage. Studies examining the NOACs in patients who require antiplatelet therapy after myocardial infarction are currently enrolling and may demonstrate the efficacy and safety of these therapies in this setting.

5 Use in Patients with Renal Dysfunction

Data from the ROCKET AF trial and subsequent post-marketing surveillance have revealed the important contribution impaired renal function makes to both stroke and bleeding risk [28]. Rivaroxaban should be avoided in patients with a CrCl of <30 ml/min, as no safety or efficacy data exists for this population and pharmacodynamic studies have shown a doubling of its anticoagulant effect [14]. Although a CrCl of <30 ml/min was an exclusion criterion in ROCKET AF, the US Food and Drug Administration (FDA) approved rivaroxaban in patients with CrCl down to 15 ml/min, based on a recommendation in their clinical pharmacology review. Their recommendation was based on a single pharmacokinetic study of 32 patients, of which only eight had severe renal failure [14]. The study demonstrated increases in the PT of 2.16-fold for moderate renal impairment (CrCl 30–49 ml/min) and 2.44-fold for severe renal impairment (CrCl < 30 ml/min), compared with patients with normal renal function. The FDA described these results as similar (as the small numbers led to statistically non-significant results) and thus approved the 15-mg dose for patients with severe renal impairment. This disregards the increased bleeding risks intrinsic to severe renal impairment [28, 29], and we believe a large clinical trial demonstrating efficacy and safety in this population should occur before widespread

use. Other regulatory bodies such as the Australian Therapeutic Goods Administration followed the exclusion criteria of the ROCKET AF trial and listed CrCl < 30 as a contraindication to rivaroxaban therapy in AF.

Regular monitoring of CrCl in patients who are taking rivaroxaban and are at risk of a silent deterioration in renal function may be warranted. Patients with a CrCl of 30–49 ml/min require a dose adjustment to 15 mg daily, as pharmacokinetic studies have demonstrated their drug levels to be around 25–50 % higher than those in patients with normal renal function [14, 30]. Importantly, in the ROCKET AF trial, patients who started on the reduced 15-mg dose were kept on that dose for the duration of the trial, unless their CrCl dropped below 30 ml/min, in which case, they discontinued the study drug permanently. Subgroup analysis of the 20 % of patients with reduced renal function showed similar results to the main group; non-inferiority with warfarin for stroke and systemic embolism in the intention-to-treat population, superiority over warfarin in patients receiving randomized treatment, and similar overall rates of bleeding [28].

Data from the ROCKET AF trial have also shown the large contribution reduced renal function makes to stroke risk. As is the general paradox in AF patients (patients with high stroke risk also have high bleeding risks), those patients with poor renal function have both an elevated bleeding and stroke risk. A subgroup analysis of the ROCKET AF data revealed patients with a CrCl of <50 ml/min had higher rates of stroke and bleeding, but the efficacy of rivaroxaban was no different in these patients compared with patients with normal renal function [28]. This subanalysis supports the non-inferiority of the reduced 15-mg daily dose of rivaroxaban for patients with a CrCl of 30–49 ml/min.

6 Bleeding Risks

Over 23,000 patients have participated in randomized trials of rivaroxaban versus warfarin for various thrombotic conditions, and all trials have shown either equivalent or reduced bleeding risks with rivaroxaban compared with warfarin. ROCKET AF showed the risk of major bleeding while taking rivaroxaban or warfarin was similar (3.6 vs. 3.4 events/100 patient-years; $P = 0.58$). Intracranial hemorrhage was rare in both groups, but slightly less in the rivaroxaban group (0.5 vs. 0.7 %; $P = 0.02$), while GI bleeding favored warfarin (3.2 vs. 2.2 %; $P = 0.001$) (see Table 1). Predictors of bleeding in patients on rivaroxaban included increasing age, baseline diastolic blood pressure ≥90 mmHg, history of chronic obstructive pulmonary disease or GI bleeding, prior aspirin use, and anemia [31]. Thirty-eight percent of patients were taking aspirin when enrolled in the trial, and, although bleeding rates were higher in this group, non-inferiority was also seen between rivaroxaban and warfarin.

7 Reversal

Warfarin's anticoagulation effects are slowly reversed by oral or parenteral vitamin K, and more rapidly with fresh frozen plasma and/or prothrombin complex concentrate. Reversal of warfarin is not without its prothrombotic risks but may be necessary in severe hemorrhage. Although the anticoagulant effects of rivaroxaban decrease substantially 24 h after a dose, a reversal agent would be desirable to enable immediate restoration of normal coagulation. No such specific reversal agent has been developed, although prothrombin complex concentrate has been reported to reverse the effect of rivaroxaban in healthy volunteers [32]. A 50-IU/kg dose of a four factor prothrombin concentrate (containing factors II, VII, IX and X) was shown to completely reverse the prolongation of the PT caused by rivaroxaban. Dialysis is not expected to effectively reverse the coagulation effects of rivaroxaban due to its high level of protein binding [30]. Unfortunately, no reversal strategies have been adequately evaluated for clinical efficacy, and current guidelines are based on expert opinion and volunteer studies as discussed above. Antidotes to reverse the anticoagulant effects of the NOACs are currently in development and are eagerly awaited.

Table 1 Bleeding rates per year in the safety on-treatment population in the ROCKET AF trial (all patients who received at least one dose of a study drug and were followed for events during the study or within 2 days after discontinuation) [19]

	Rivaroxaban ($n = 7111$) (%)	Warfarin ($n = 7125$) (%)	NNT/NNH	HR (95 % CI)
Major bleeding	3.6 (395)	3.4 (386)	Not applicable	1.04 (0.90–1.2)
Gastrointestinal bleeding	3.2 (224)	2.2 (154)	NNH = 100	$P < 0.001$; HR not specified
Intracranial bleeding	0.5 (55)	0.7 (84)	NNT = 250	0.67 (0.47–0.93)
Major and non-major clinically relevant bleeding	14.9 (1475)	14.5 (1449)	Not applicable	1.03 (0.96–1.11)

CI confidence interval, *HR* hazard ratio, *NNT/NNH* number needed to treat/harm

8 Temporary Interruptions and Perioperative Management

Temporary interruption to anticoagulant therapy is commonly required, either to allow therapeutic procedures to be performed or when significant bleeding occurs. Temporary interruptions were common in the ROCKET AF trial, with a third of patients discontinuing their study medication for a median of 5 days [33]. Reasons for interruptions were varied, with 40 % undergoing a surgical or invasive procedure, 25 % stopping their medication due to an adverse event unrelated to bleeding and 13 % for an adverse bleeding event. The remaining 12 % were due to subject error, or other logistical difficulties related to the trial. Stroke risk during the 30 days after rivaroxaban interruption was significant, with a stroke/systemic embolism rate of 0.3 % or 1 in 333 interruptions. Bleeding risks were also significant, with 1 % of all interruptions being complicated with a major bleeding episode. This was true for both the group that underwent a surgical procedure and those that stopped for other reasons.

Although initial results of the main ROCKET AF trial suggested higher rates of both thrombotic and bleeding adverse events after stopping rivaroxaban (when compared with stopping warfarin), two separate analyses have shown otherwise [33, 34]. The initial signal came from the observation that more adverse events occurred in the rivaroxaban group after the trial finished, during the transition to open-label warfarin. Further analysis, however, has shown that there were no significant differences between the rivaroxaban and warfarin groups in the rates of stroke or systemic embolism after temporary interruption or early, permanent study drug discontinuation (rivaroxaban, $n = 51$; warfarin, $n = 44$; 16.49 vs. 14.05 events per 100 patient-years; HR 1.21; 95 % CI 0.81–1.81; $P = 0.35$). There were significantly more bleeding and thrombotic events in rivaroxaban-treated patients during the month after the trial, during which these patients were transitioned to open-label warfarin, and patients treated with warfarin were continued on vitamin K antagonist therapy. This reflects the danger associated with transitioning from one anticoagulant to another (not an increased risk of stopping rivaroxaban), and underscores the importance of careful attention to this period.

Only 9 % of interruption episodes in the ROCKET AF trial involved bridging therapy, the majority with low molecular weight heparin. Theoretically, the rapid onset and offset of rivaroxaban may offer an advantage during interruptions, as bridging may be unnecessary. However, the risk profile of bridging with parenteral anticoagulants is not well established and no clear consensus currently exists as to the risks and potential benefits of bridging therapy [33–36].

When considering the perioperative management of patients taking anticoagulants, a widely used approach involves assessment of the thromboembolic risk of medication cessation and evaluation of the bleeding risk of the procedure. If the bleeding risks involved in continuing anticoagulation throughout are deemed excessive, a plan for interruption and reinstitution of anticoagulation is required [37]. Many procedures (e.g., most dental procedures, pacemaker implantations, cutaneous procedures) can be safely performed without anticoagulation interruption. In fact, several studies have demonstrated lower embolic and bleeding complications in patients who continue their anticoagulant medication (warfarin in these studies) as compared with in those who stop and are bridged with heparin [38, 39]. For procedures where the bleeding risk associated with continuing anticoagulation is thought excessive, stopping rivaroxaban three doses before high bleeding risk surgery, and two doses before low bleeding risk surgery is recommended, although this is based on expert opinion [40].

When utilizing neuraxial anesthesia, current guidelines recommend 22–26 h between the last dose of rivaroxaban and spinal or epidural puncture in patients with normal renal function. Longer intervals are required in those with reduced renal function [41]. Although these recommendations concern the 10-mg dose, and little clinical data exists for the AF doses (20 and 15 mg), pharmacodynamic data suggest similar time intervals should be sufficient (24 h for patients with normal renal function and 48–72 h for patients with decreased renal function) [11]. Indwelling neuraxial catheters should not be used concurrently with rivaroxaban as available experience in this area is very limited. No direct patient data exist to guide practice in this area, and recommendations may change with the upcoming release of the American Society of Regional Anesthesia's 4th anticoagulation guidelines. Given rivaroxaban's rapid onset of action, adequate hemostasis should be obtained before restarting rivaroxaban post-operatively. For low bleeding risk surgery, it can usually be given on the first day after surgery, while 4–6 h are required between spinal block and initiation of rivaroxaban post-operatively [41]. In high bleeding risk situations, some groups utilize prophylactic dose low molecular weight heparin for 2–4 days post-surgery before restarting rivaroxaban.

9 Conclusion

Rivaroxaban, a new direct-acting, orally active anticoagulant, offers an alternative to warfarin for stroke prevention in patients with non-valvular AF. Its strengths include a once daily dose that does not require routine coagulation

monitoring, and minimal dietary restrictions and lower rates of intracranial hemorrhage. Its disadvantages include the need for strict adherence to daily therapy, the lack of a reversal agent and a higher incidence of GI bleeding. The current evidence suggests rivaroxaban is a useful alternative to warfarin in a large proportion of AF patients, and with the other novel anticoagulants, offers patients similar degrees of stroke protection and overall bleeding risks with more convenience than warfarin.

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