



## The Use of Rivaroxaban in Nonvalvular Atrial Fibrillation

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**A**trial fibrillation affects approximately 2.5 million people in the United States. People over the age of 40 years have a 25% chance of developing atrial fibrillation during their lifetime. Moreover, the risk of developing atrial fibrillation increases proportionately with age. The prevalence of atrial fibrillation in people aged greater than 80 years is approximately 10%.<sup>1,2</sup> By 2050, the prevalence of atrial fibrillation has been predicted to increase 2.5-fold to approximately 6 million people, reflecting the growing population of elderly people.<sup>3</sup>

Persons with atrial fibrillation are at a five-fold increased risk of ischemic stroke compared to those without atrial fibrillation.<sup>4</sup> Additionally, atrial fibrillation accounts for approximately 15% of strokes in people of any age and 30.7% in people 80-89 years old.<sup>4,5</sup>

Primary treatment strategies for atrial fibrillation include rhythm and rate control. Rhythm can be controlled by chemical or electrical cardioversion, whereas rate control can be accomplished by the use of medications or atrioventricular (AV) node ablation.<sup>6,7</sup> People who are being treated with rate control and those being treated with rhythm control that are at an increased risk for clots should also be treated with an anticoagulant.<sup>7</sup>

Warfarin has been considered the standard therapy for the prevention of stroke and remains the most commonly used anticoagulant to date. Warfarin decreases the risk of ischemic stroke or non-CNS embolism (systemic embolisms) to 1.66% per year.<sup>8</sup> However, there are numerous limitations with the use of warfarin. First, warfarin interacts with many drugs through the cytochrome P450 system. These interactions could result in a person being under- or over-anticoagulated. Secondly, vitamin K, which is found in numerous foods, is a cofactor in the production of clotting factors.<sup>9</sup> Therefore, changes in vitamin K consumption can impact the effectiveness and safety of warfarin. Third, warfarin has a narrow therapeutic window, which warrants frequent INR monitoring throughout the duration of therapy. Due to these limitations, there is a need for the further development of new anticoagulant medications.

Rivaroxaban (Xarelto<sup>®</sup>) is an orally bioavailable direct factor Xa inhibitor approved by the FDA in 2011 for DVT prophylaxis after knee or hip surgery and later for prevention of stroke and systemic embo-

### Editor's Summary: Rivaroxaban

#### Description & Indication

- ◆ Oral factor Xa inhibitor (anticoagulant/antithrombotic)
- ◆ Indicated for stroke prophylaxis in patients with nonvalvular atrial fibrillation (AF) and for DVT prophylaxis

#### Dosing

- ◆ For AF, dosed 20 mg once daily (or 15 mg once daily if CrCL < 50 mL/min); avoid if CrCL < 15 mL/min

#### Efficacy

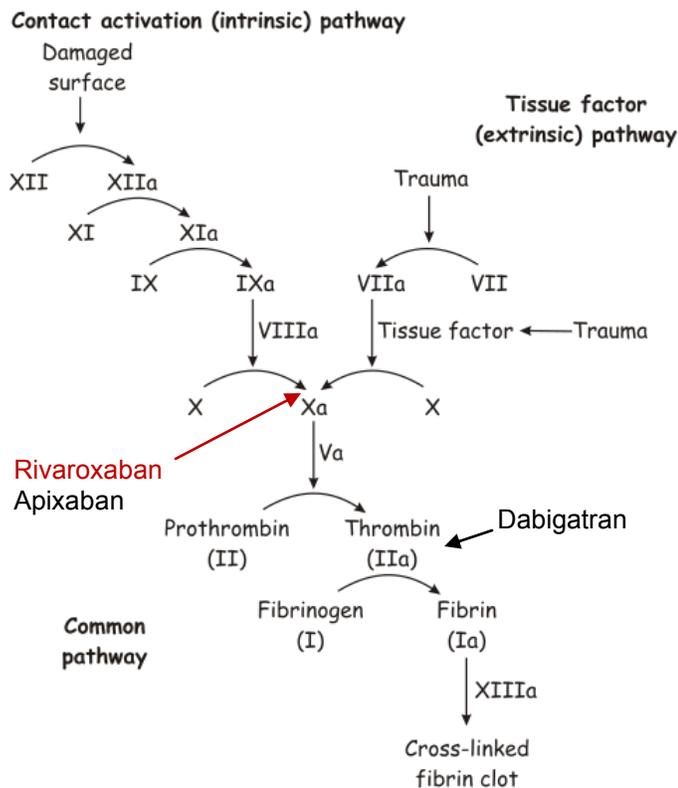
- ◆ Non-inferior to dose-adjusted warfarin in reducing cardioembolic stroke
- ◆ Possibly superior to warfarin, but warfarin management was relatively poor in the ROCKET AF trial

#### Safety

- ◆ Similar overall bleeding risk to warfarin, but lower risk of critical or fatal bleeds with rivaroxaban in ROCKET AF

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**Figure 1. The intrinsic and extrinsic pathways of the clotting cascade. Rivaroxaban acts on the active site of factor Xa, preventing the downstream conversion of Prothrombin to Thrombin.**

lism in people with nonvalvular atrial fibrillation.<sup>10,11</sup> The purpose of this article is to summarize the pharmacology, pharmacokinetics, pharmacodynamics, and efficacy and safety of rivaroxaban use in patients with atrial fibrillation.

## PHARMACOLOGY & PK/PD PARAMETERS

Rivaroxaban selectively blocks the active site of factor Xa and doesn't require a cofactor (substances that promote the clotting factor cascade) for activity (Figure 1). The inhibition of factor Xa is dose-dependent resulting in prolongation of the prothrombin time and aPTT, with the magnitude of prolongation depending on the dose.<sup>10,11</sup> In contrast, warfarin inhibits vitamin K dependent factors II, VII, IX, X, and anticoagulant proteins C and S. Once Rivaroxaban blocks the active site of factor Xa, thrombin and fibrin can't be formed, thereby preventing the formation of clots. Since rivaroxaban doesn't inhibit vitamin K-dependent factors, vitamin K containing foods have no effect on rivaroxaban's effectiveness as an anticoagulant.<sup>12</sup> Furthermore, rivaroxaban may provide more consistent and predictable anticoagulation compared to

warfarin.<sup>5</sup> The median inhibition of factor Xa ranges from 20% to 61% with 5 mg to 80 mg tablet dosing. After the administration of rivaroxaban, the maximum inhibition of factor Xa occurs in 1-4 hours and peak plasma concentrations are reached after a minimum of 2 hours.<sup>13</sup> In healthy adults aged 20-45 years, the half-life of rivaroxaban is 5-9 hours. However, the half-life in elderly people is 11-13 hours.<sup>10</sup> Other pharmacokinetic properties of rivaroxaban are listed in Table 1.

## CLINICAL TRIALS

### Efficacy

The ROCKET AF study was a multicenter, randomized, double-blind, double-dummy, event-driven trial that enrolled 14,264 patients with persistent or paroxysmal atrial fibrillation. Patients had to have a history of stroke/TIA, systemic embolism, or >2 of the following: chronic heart failure or left ventricular ejection fraction  $\leq 35\%$ , hypertension, age  $\geq 75$  years, or diabetes. However, patients that had a prosthetic heart valve, planned cardioversion, atrial fibrillation secondary to a reversible disorder, active bleed, known presence of atrial myxoma or left ventricular thrombus, or those with an increased bleeding risk (active internal bleeding, chronic hemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm, planned invasive procedure with potential for uncontrolled bleeding, history of intracranial, intraocular, spinal, or atraumatic intraarticular bleeding, clinically significant gastrointestinal bleeding within 6 months, and major surgical procedures or trauma within 30 days before randomization) were excluded from the study. Other exclusion criteria include pregnancy, anemia, any stroke within 14 days before randomization, TIA within 3 days of randomization and treatment with aspirin, NSAIDs, and strong inhibitors and inducers of cytochrome P450 3A4. Additional exclusion criteria are listed in Table 2. Patients were randomly assigned to treatment with a placebo pill along with oral doses of either rivaroxaban (N = 7131) 20mg daily (15mg daily if the patient had a CrCl between 30-49 mL/min) or warfarin (N = 7133) adjusted-dosing to a target INR range of 2.0-3.0. The primary outcome, a composite of ischemic or hemorrhagic stroke and systemic embolism, occurred in 188 patients (1.7%) in the rivaroxaban group and in 241 patients (2.2%) in the warfarin group (HR 0.79; 95% CI 0.66-0.95; non-inferiority  $p \leq 0.001$ ). Because non-inferiority was achieved, superiority in the safety population was tested. In the per-protocol (as-treated) analysis, rivaroxaban was superior to warfarin in preventing stroke and systemic embolism.

**Table 1 | Pharmacokinetics of rivaroxaban.**<sup>9,10</sup>

<b>Absorption</b>	<ul style="list-style-type: none"> <li>• Oral bioavailability (dose dependent): 66%-100%</li> <li>• Effects of food (10mg): no effect</li> <li>• Effects of food (20mg): AUC increase by 39%, Cmax increase by 76%</li> <li>• Cmax: 2-4 hours</li> <li>• Interactions with drugs altering gastric pH: no effect on bioavailability when combined with ranitidine (150mg BID), aluminum/magnesium hydroxide (10mL), and omeprazole (40mg daily)</li> </ul>
<b>Distribution</b>	<ul style="list-style-type: none"> <li>• Plasma protein binding: 92%-95%</li> <li>• Vd: 50 L</li> </ul>
<b>Metabolism</b>	<ul style="list-style-type: none"> <li>• 51% of drug recovered as metabolites in the urine</li> <li>• Oxidative degradation catalyzed by CYP3A4/5, CYP2J2, and hydrolysis</li> </ul>
<b>Excretion</b>	<ul style="list-style-type: none"> <li>• Renal clearance: 2.4 L/hr and 0.5-1.2 L/hr in renal impairment</li> <li>• Renal: 66%, 36% unchanged</li> <li>• Fecal: 28%, 7% unchanged</li> <li>• Unchanged drug excreted in the urine via active tubular secretion and glomerular filtration (5:1 ratio)</li> <li>• Systemic clearance: 10 L/hr and 4.5-5.4 L/hr in renal impairment</li> <li>• T<sub>1/2</sub>: 5-9 hrs in healthy subjects, 11-13 hrs in elderly, 8.7-9.5 hrs in renal impairment</li> </ul>

There were 189 events in the rivaroxaban group and 243 events in the warfarin group, resulting in a HR of 0.79 (95% CI 0.65-0.95; superiority  $p < 0.001$ ). No statistically significant difference in the occurrence of MI or death between the two treatment groups was observed. Also, no statistically significant difference in the primary outcome rate was observed between the two drugs after treatment discontinuation.

The ROCKET AF trial several noteworthy limitations. First, the patients taking warfarin only spent an average of approximately 55% of the time in the therapeutic range (TTR). In previous large-scale trials of warfarin in atrial fibrillation, the TTR for warfarin-treated patients has generally fallen within the range of 60-70%. Thus, the superiority of rivaroxaban over warfarin may be a result of inadequate management among warfarin-treated patients in ROCKET AF. Secondly, the use of aspirin was allowed during the study, although the distribution was fairly even between the two groups. Approximately 34.9% of patients in the rivaroxaban group and 36.2% in the warfarin group reported the use of aspirin. Concurrent use of aspirin can increase the bleeding risk and potentially skew the safety results. Approximately 62% of patients reported previous use of vitamin K antagonists. If patients had any previous adverse events with warfarin and they experience similar events during the study, they may assume they are taking warfarin and unfortunately change their eating habits. A diet that has a consistent amount of vitamin K would be an advantage for warfarin patients. Patients with a CrCl  $< 30$  mL/min were excluded from the study. However, rivaroxaban is approved in patients with a CrCl as low as 15

mL/min. Furthermore, the study only included patient with a CHADS<sub>2</sub> score  $\geq 2$ . Patients that enrolled in the study that didn't have a previous thromboembolism who had a CHADS<sub>2</sub> score of 2 were intentionally limited to 10%. All other patients had to have a previous thromboembolism or CHADS<sub>2</sub>  $\geq 3$ . Therefore, the result of the ROCKET AF trial may or may not be as relevant for patients currently at a lower risk for stroke. When the study was terminated, 23.7% of patients taking rivaroxaban and 22.2% of patients taking warfarin had already discontinued their medication before an end-point event had occurred. The ending population of patients taking the two drugs is smaller than the starting population, therefore, the power of the study will be reduced.<sup>5</sup>

### Safety

The primary safety outcome was a composite of major and non-major clinically relevant bleeding events. **Table 3** includes various bleeding rates that were reported in the ROCKET AF trial. The primary safety outcome occurred in 1475 patients (14.9%) in the rivaroxaban group and in 1449 patients (14.5%) in the warfarin group (HR 1.03; 95% CI 0.96-1.11;  $p = 0.44$ ). Compared to warfarin, rivaroxaban had a decreased rate of critical bleeding (HR 0.69; 95% CI 0.53-0.91;  $p = 0.007$ ) and fatal bleeding (HR 0.50; 95% CI 0.31-0.79;  $p = 0.003$ ). Bleeds were considered to be critical if they were intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular, or in retroperitoneal sites. Critical bleeds occurred in 91 patients (1.3%) taking rivaroxaban and in 133 patients (1.9%) taking warfarin. Fatal bleed occurred in 27 patients

Table 2 | Details of the ROCKET AF Trial.<sup>5</sup>

Study	Enrollment & Design	Dosing Schedule	Inclusion/Exclusion	Primary/Secondary Outcomes & Results
ROCKET AF	<p>N = 14,264</p> <p>Multicenter, R, DB, double-dummy, event-driven trial</p>	<p><b>Rivaroxaban:</b></p> <ul style="list-style-type: none"> <li>N = 7,131</li> <li>20mg daily (15mg daily in pts with CrCl of 30-49 ml/min) plus placebo</li> </ul> <p><b>Warfarin:</b></p> <ul style="list-style-type: none"> <li>N = 7,133</li> <li>Adjusted-dosing to target INR of 2-3 plus placebo</li> </ul>	<p><b>Inclusion:</b></p> <ul style="list-style-type: none"> <li>≥18 years old</li> <li>Nonvalvular a-fib at moderate/high risk of stroke</li> <li>Increased risk included pts with history of stroke, TIA, systemic embolism, <b>OR</b> &gt;2 of the following: congestive heart failure and/or LVEF &lt;35%, HTN, age ≥75 years, DM (CHADS<sub>2</sub> ≥2)</li> </ul> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>A-fib and hemodynamically significant mitral stenosis or any valve prostheses</li> <li>Transient atrial fibrillation caused by a reversible disorder</li> <li>Indication for anticoagulant therapy other than atrial fibrillation</li> <li>Excessive hemorrhagic risk</li> <li>Active endocarditis</li> <li>Planned cardioversion</li> <li>Stroke within 14 days and TIA within 3 days of randomization</li> <li>Current/planned treatment with a drug that is a strong inhibitor or inducer of CYP3A4</li> <li>ASA&gt;100mg daily</li> <li>Anticipated need for long-term treatment with NSAID</li> <li>Pregnancy or breastfeeding</li> <li>Anemia (hemoglobin &lt;10 g/dL)</li> <li>CrCl &lt;30 ml/min. at screening visit</li> <li>Known HIV</li> </ul>	<p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>Composite of stroke (ischemic or hemorrhagic) and systemic embolism</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>Composite of stroke, systemic embolism, death from CV causes, or MI</li> <li>Individual components of each composite</li> </ul> <p><b>Results:</b></p> <p><i>Primary outcomes:</i></p> <ul style="list-style-type: none"> <li>Occurred in 188 rivaroxaban pts &amp; 241 warfarin pts (HR 0.79; 95% CI 0.66-0.95; non-inferiority p≤0.001)</li> </ul> <p><i>Per-protocol (as-treated) safety population:</i></p> <ul style="list-style-type: none"> <li>Occurred in 189 rivaroxaban pts &amp; 243 warfarin pts (HR 0.79; 95% CI 0.65-0.95; superiority p = &lt;0.001)</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>MI occurred in 101 rivaroxaban pts &amp; 126 warfarin patients (HR 0.81; 95% CI 0.63-1.06; p =0.12)</li> <li>Death occurred in 208 rivaroxaban pts &amp; 250 warfarin pts (HR 0.85; 95% CI 0.70-1.02; p=0.07)</li> </ul>

**N** = number of patients; **R** = randomized; **DB** = double-blind; **LVEF** = left ventricular ejection fraction; **TIA** = transient ischemic attack; **DM** = diabetes mellitus; **CV** = cardiovascular; **pt(s)** = patient(s); **MI** = myocardial infarction.

**Table 3 | Bleeding Events in ROCKET AF Trial.<sup>5</sup>**

Bleeding Type	Rivaroxaban (N = 7111) No. (%)	Warfarin (N = 7125) No. (%)	Hazard Ratio (95% CI)	P Value
Major & non-major clinically relevant bleedings <sup>a</sup>	1475 (20.7)	1449 (20.3)	1.03 (0.96-1.11)	0.44
Major bleeding				
Any	395 (5.6)	386 (5.4)	1.04 (0.90-1.20)	0.58
Decreased in Hemoglobin $\geq 2$ g/dl	305 (4.3)	254 (3.6)	1.22 (1.03-1.44)	0.02
Transfusion	183 (2.6)	149 (2.1)	1.25 (1.01-1.55)	0.04
Critical bleeding	91 (1.3)	133 (1.9)	0.69 (0.53-0.91)	0.0007
Fatal bleeding	27 (0.4)	55 (0.8)	0.50 (0.31-0.79)	0.003
Intracranial hemorrhage	55 (0.8)	84 (1.2)	0.67 (0.47-0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	1151 (16.2)	1.04 (0.96-1.13)	0.35

<sup>a</sup> Primary safety endpoint.

(0.4%) taking rivaroxaban and in 55 patients (0.8%) taking warfarin. Major bleed from a gastrointestinal site was more common in the rivaroxaban group (224 events, 3.2%) compared to the warfarin group (154 events, 2.2%) with  $p < 0.001$ .<sup>5</sup>

Non-bleeding adverse events of rivaroxaban, include headache, ecchymosis, and the taste of blood. Headaches were relieved with analgesic therapy. In those tasting blood, there was no actual blood present in the mouth and the sensation resolved within 30-105 minutes.<sup>13</sup> The risk of syncope with rivaroxaban is approximately 1.2%.<sup>11</sup> Adverse events that can occur with rivaroxaban when used for DVT prophylaxis after knee or hip surgery include wound secretions, pain in the extremity, muscle spasm, and pruritus.<sup>10</sup>

### DOSING

Currently rivaroxaban is indicated for cardioembolic stroke prevention in patients treated for nonvalvular atrial fibrillation that have a CrCl  $>15$  mL/min. In patients with normal renal function, rivaroxaban should be administered as a single 20 mg daily dose with the evening meal. Patients CrCl between 15 and 50 mL/min should take 15 mg once daily. Rivaroxaban should be avoided in patients with a CrCl  $<15$  mL/min. Riva-

roxaban should be avoided in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. Drugs that are strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, conivaptan, clarithromycin, erythromycin, and fluconazole) and inducers (carbamazepine, phenytoin, rifampin, and St. john's wort) may interfere with rivaroxaban exposure. Therefore, concomitant use of rivaroxaban and these medications should be avoided if possible. Do not administer rivaroxaban via feeding tube or other method that could deposit the drug directly into the proximal small intestine. This method of administration will result in decreased absorption and drug exposure.<sup>10</sup> Unlike warfarin, rivaroxaban doesn't require INR monitoring.

### COST

A patient's cash price of rivaroxaban, not using insurance, can vary depending on the pharmacy. Current approximate prices for rivaroxaban and warfarin are listed in **Table 4**. The price for each drug is based on thirty tablets for a thirty day supply. For comparison, the table also includes the price range for warfarin plus the price for INR testing that is done at the UM Lowry clinic. The total cost for new patients for an

**Table 4 | Cash prices for Rivaroxaban and Warfarin (30 days supply).**

Pharmacy	Rivaroxaban 20mg	Rivaroxaban 15mg	Warfarin	Warfarin + INR (1 test/month)
Walgreens	\$282.99	\$274.09	\$17 to \$27	\$92 to \$277
King Soopers	\$246.69	Not available	\$4	\$79 to \$254
Target	\$284.99	\$251.99	\$4	\$79 to \$254
UM Lowry Pharmacy	\$266.81	\$266.81	\$20.75 to \$31.17	\$95.75 to \$281.17

anticoagulation visit and INR lab is \$250, whereas a returning patient would be charged \$150 for the same service. The cost of the INR test alone is \$75. An INR test may need to be done more than once a month in warfarin-treated patients, which will increase the price for the patient. However, this pricing is only an estimate of cost associated with in-clinic management of warfarin. Some patients may have lower long-term costs by self-testing using a home point-of-care device.<sup>14</sup> Addition information on INR home testing is available online (<http://www.clotcare.com/pst.aspx>).

In general, patients who require infrequent INR monitoring while on warfarin will usually have lower associated monetary costs with continuing warfarin than switching to rivaroxaban. However, warfarin-treated patients requiring frequent INR monitoring may find rivaroxaban therapy a less expensive option.

### CONCLUSION

Rivaroxaban is an orally bioavailable direct factor Xa inhibitor that doesn't require a cofactor for activity. The medication is indicated for DVT prophylaxis post knee and hip surgery, and for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Patients with atrial fibrillation and normal renal function should take 20 mg once daily (or 15 mg for patients with a CrCl between 15 and 50 mL/min) with the evening meal. Rivaroxaban is non-inferior to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation. However, the patients enrolled in the ROCKET AF study were at a moderate to high risk for stroke (CHADS<sub>2</sub> ≥2) and this study may not be generalizable to patients at lower risk of cardioembolic stroke. Furthermore, only 10% of these patients had a CHADS<sub>2</sub> score of 2. Overall bleeding risk with rivaroxaban appears similar to warfarin. Rivaroxaban has a decreased risk for critical bleed, fatal bleed, and intracranial hemorrhage. However, compared with warfarin, rivaroxaban is associated with a slight increase in the risk of gastrointestinal site bleeding, bleeding resulting in a drop in the hemoglobin level, and bleeding resulting in the need for a transfusion.

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