

# THE BENEFITS OF RIVAROXABAN (XARELTO®) ACROSS MULTIPLE INDICATIONS AND THE RELEVANCE TO CARDIOLOGISTS

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## ABSTRACT

Oral anticoagulation with vitamin-K-antagonists has well known limitations and requires routine clinical monitoring of coagulation parameters. The new oral anticoagulants represent novel direct-acting inhibitors of the coagulation factors IIa (thrombin) or Xa. The compound with the currently widest clinical approval for oral anticoagulation in the group of the Xa inhibitors (also known as the -xabans) is the direct oral factor Xa inhibitor rivaroxaban (Xarelto®). Rivaroxaban was the first direct factor Xa inhibitor with clinical approval for long-term oral anticoagulation in patients with non-valvular atrial fibrillation and has since gained additional approval for the treatment and prevention of deep vein thrombosis and pulmonary embolism. Furthermore, low-dose rivaroxaban, in addition to standard antiplatelet therapy, has been shown to reduce cardiovascular mortality in patients following a recent acute coronary syndrome and recently gained approval for the prevention of atherothrombotic events after acute coronary syndrome by the European Medicines Agency (EMA). This review article discusses the clinical use and benefits of rivaroxaban for multiple indications.

**Keywords:** Rivaroxaban, novel oral anticoagulants, atrial fibrillation, deep vein thrombosis, pulmonary embolism, acute coronary syndrome.

## NOVEL ORAL ANTICOAGULANTS

The introduction of new oral anticoagulants (NOACs) has been eagerly awaited for decades, as the choice of anticoagulation has been restricted to vitamin-K-antagonists, which have well-known shortcomings. With the approval of the direct factor IIa (thrombin) inhibitor dabigatran and the direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) for a variety of clinical indications where oral anticoagulation is deemed necessary, there are now drugs available that may be easier to use compared to vitamin-K-antagonists and more importantly these drugs significantly lower the risk for life-threatening intracranial bleeding events.<sup>1,2</sup> Among the factor Xa inhibitors (also named the -xabans), rivaroxaban was the first of its class to gain clinical approval for the use as an oral anticoagulant for stroke prevention in patients

with non-valvular atrial fibrillation (AF) and for the acute treatment of deep vein thrombosis (DVT) and secondary prevention of recurrent venous thromboembolism (VTE) in 2011. Soon thereafter, rivaroxaban was also approved for the acute treatment of pulmonary embolism (PE) and secondary prevention of recurrent VTE in 2012. Very recently, in 2013, the European Medicines Agency (EMA) approved twice-daily low-dose rivaroxaban in combination with standard antiplatelet therapy for secondary prevention of atherothrombotic events in patients that suffered from a recent acute coronary syndrome (ACS).

## DIRECT INHIBITION OF FACTOR Xa WITH RIVAROXABAN

Any new oral anticoagulant has undergone an extensive phase of clinical development, which

always includes the clinical scenarios with the highest risk for thromboembolism. This is especially given after total knee and hip replacement surgery, therefore it is understandable that clinical trials in patients undergoing this surgery were the starting points for each of the novel oral anticoagulants. Rivaroxaban has been assessed in the extensive RECORD 1-4 clinical study program in 12,729 patients undergoing either elective total knee or hip replacement surgery. Across the RECORD studies, a 10 mg once-daily dose of rivaroxaban was used to prevent VTE compared to 40 mg once-daily (30 mg twice-daily in RECORD 4) enoxaparin. Rivaroxaban demonstrated superiority over enoxaparin for the prevention of total VTE and was clinically approved for this indication in 2008.<sup>2-6</sup>

The small molecule direct factor Xa inhibitor rivaroxaban has a high oral bioavailability and a competitive mechanism of binding to factor Xa. The affinity of rivaroxaban to factor Xa is >10,000-fold greater as compared to other serine proteases thereby potentially inhibiting the conversion of prothrombin to thrombin which occurs downstream of factor Xa activation within the coagulation cascade. The maximum inhibition of factor Xa occurs within 3 hours of oral intake<sup>7,8</sup> corresponding to maximum plasma concentrations reached 2-4 hours after oral administration. The elimination of rivaroxaban occurs partially via the kidney (one third is excreted unchanged) and the mean terminal half-life after multiple oral doses is between 7-11 hours.<sup>7,8</sup> The anticoagulative effects of rivaroxaban in human plasma may be detected by the prothrombin time (PT), but results are variable depending on the reagents used for the clotting assays and the timing of blood sampling after oral intake.

## ORAL ANTICOAGULATION WITH RIVAROXABAN ACROSS MULTIPLE INDICATIONS

### Atrial Fibrillation

Rivaroxaban is clinically approved for the prevention of stroke or systemic embolism in patients with non-valvular AF with one or more risk factors such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke, or transient ischaemic attack. Patients with AF requiring oral anticoagulation

should receive 20 mg rivaroxaban once-daily. Routine measurement of coagulation parameters is not necessary when patients are treated with rivaroxaban. A reduced dose of 15 mg once-daily rivaroxaban has been specifically and successfully tested and should be used in patients with impaired renal function (creatinine clearance 15-49 ml/min).<sup>9</sup> Rivaroxaban should be used with caution in patients with a creatinine clearance of 15-29 ml/min and should not be used in patients with a creatinine clearance  $<15$  ml/min.

Rivaroxaban is not recommended in patients with mechanical heart valves that require anticoagulation. There are limited interactions with concomitant medication; these include strong inhibitors of CYP3A4 and P-glycoprotein that lead to increased plasma concentrations of rivaroxaban which are therefore not recommended, and with any other anticoagulant as it may increase the bleeding risk and which is therefore contraindicated. Due to limited clinical and safety data, the concomitant use of dronedarone with rivaroxaban is not recommended.

The randomised, double-blind clinical Phase III trial ROCKET AF led to the approval of rivaroxaban for stroke prevention in AF and comprised 14,264 patients with non-valvular AF and a moderate-to-high risk for stroke or systemic embolism (mean CHADS<sub>2</sub> score of 3.5).<sup>10</sup> In ROCKET AF patients were either randomised to rivaroxaban 20 mg once-daily (or to 15 mg once-daily in case of a creatinine clearance of 30-49 ml/min), or to dose-adjusted warfarin. Treatment was blinded with mock INR values in the rivaroxaban group. The composite primary efficacy endpoint of ROCKET AF was all-cause stroke and non-central nervous system systemic embolism. In the primary analysis of the per-protocol on-treatment population, the event rates for the primary efficacy endpoint were 1.7 and 2.2 per 100 patient-years for rivaroxaban and warfarin, respectively ( $p < 0.001$  for non-inferiority in this population and  $p = 0.02$  for superiority in the pre-specified analysis of the safety on-treatment population).<sup>10</sup> The primary safety outcome of major and non-major clinically relevant bleedings was similar in both treatment groups. Major bleeding events occurred with a rate of 3.6 and 3.4 per 100 patient-years ( $p = 0.44$ ) in the rivaroxaban and warfarin treated patients, respectively. However, decreases in haemoglobin

levels of  $\geq 2$  g/dl and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding into critical anatomical sites were less frequent. Rates of intracranial haemorrhage were also significantly lower in the rivaroxaban group than in the warfarin group (rivaroxaban 0.5 versus warfarin 0.7 per 100 patient-years,  $p=0.02$ ).<sup>10</sup>

## Deep Vein Thrombosis

The acute treatment of DVT requires immediate sufficient anticoagulation to prevent further thrombus growth and embolisation. The prevention of VTE after DVT requires oral anticoagulation for a duration of several months, depending on the individual's risk for a recurrence, outbalanced against the individual's bleeding risk. Before the introduction of rivaroxaban for the treatment and prevention of DVT, initial anticoagulation required the use of parenteral anticoagulation (e.g. unfractionated heparin, enoxaparin, or fondaparinux) followed by a VKA. With the approval of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE, it is now possible to initiate treatment immediately with an oral anticoagulant without the need for initial parenteral anticoagulation. The recommended dose of rivaroxaban for the treatment of acute DVT is 15 mg twice-daily for a period of 3 weeks. Thereafter, oral anticoagulation is continued with a once-daily dose of 20 mg of rivaroxaban.<sup>2</sup>

The clinical approval of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT or PE is based on the results of the randomised Phase III open label EINSTEIN-DVT trial. A total of 3,449 patients with acute symptomatic DVT were randomised in EINSTEIN-DVT to either rivaroxaban 15 mg twice-daily for 3 weeks followed by once-daily rivaroxaban 20 mg for a duration of 3, 6, or 12 months, or weight-adjusted enoxaparin twice-daily for a minimum of 5 days followed by dose-adjusted vitamin-K-antagonist.<sup>11</sup> The primary efficacy endpoint of symptomatic recurrent VTE occurred in 2.1% of rivaroxaban treated patients versus 3.0% of enoxaparin plus vitamin-K-antagonist treated patients ( $p<0.001$  for non-inferiority). Rates of major plus non-major clinically relevant bleedings, the primary safety outcome, were similar in both groups. Rates of major bleedings were also similar in both groups (0.8% and 1.2% for rivaroxaban- and

enoxaparin plus vitamin-K-antagonist-treated patients, respectively,  $p=0.21$ ).<sup>11</sup>

## Pulmonary Embolism

Pulmonary embolism relies on the formation of venous thrombi and is therefore often accompanied by the clinical evidence for DVT. In contrast to asymptomatic DVT, PE can be a life-threatening event, therefore an immediate and reliable anticoagulation therapy is deemed necessary. Rivaroxaban as a single oral anticoagulant drug (without the need for additional initial parenteral anticoagulants) has gained clinical approval for the treatment of PE and the prevention of recurrent DVT or PE, if the patient is haemodynamically stable and does not require systemic lysis therapy. In this indication, rivaroxaban is administered at a dose of 15 mg twice-daily for a period of 3 weeks following acute PE. Thereafter oral anticoagulation is continued with a single 20 mg daily dose of rivaroxaban.

The EINSTEIN PE trial was the clinical Phase III assessment leading to the approval of rivaroxaban as a single oral anticoagulant for the treatment of PE and the prevention of DVT or PE. In EINSTEIN PE, 4,832 patients with acute PE (with or without DVT) were randomised to either oral anticoagulation with rivaroxaban 15 mg twice-daily for 3 weeks followed by 20 mg once-daily for 3, 6, or 12 months, or to weight-adjusted enoxaparin twice-daily for a minimum of 5 days followed by oral anticoagulation with a vitamin-K-antagonist.<sup>12</sup> The event rates for the primary efficacy endpoint of symptomatic recurrent VTE were 2.1 versus 1.8 ( $p=0.003$  for non-inferiority) in the rivaroxaban and enoxaparin plus vitamin-K-antagonist treated patients, respectively. While there were no significant differences in the composite primary safety outcome of major bleedings plus non-major clinically relevant bleedings (10.3% versus 11.4% for rivaroxaban and enoxaparin plus vitamin-K-antagonist treatment, respectively,  $p=0.23$ ) there was a significant reduction of major bleeding events in the rivaroxaban treated patient group (1.1% versus 2.2% for rivaroxaban versus enoxaparin plus vitamin-K-antagonist, respectively,  $p=0.003$ ).<sup>12</sup>

## Acute Coronary Syndrome

Major determinants of the long-term clinical outcome after an ACS in patients undergoing percutaneous coronary intervention and stent implantation, are recurrent acute coronary artery occlusion/stenosis and major bleeding events under antithrombotic therapy. While the ischaemic cardiovascular event rates were dramatically reduced following the clinical introduction of the second generation (clopidogrel) and third generation (prasugrel and ticagrelor) P2Y12 antagonists,<sup>13</sup> there is still an unmet need for an optimal antithrombotic regimen (consisting of dual antiplatelet and anticoagulant therapy) in patients with ACS as residual rates of recurrent cardiovascular events despite therapy are still high. The major obstacle of antithrombotic therapy in ACS is the increase in bleeding risk, especially in older patients, caused by the synergy of dual antiplatelet therapy and anticoagulant therapy. An ideal antithrombotic therapy in patients with ACS would provide an effective inhibition of platelet activation and attenuation of the coagulation system without an accompanying increase in bleeding. An attenuation of the coagulation system could be provided by the recently EMA approved low-dose (2.5 mg twice-daily) rivaroxaban therapy, to be co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, in patients after an ACS with elevated cardiac biomarkers.

The randomised, double-blind ATLAS ACS 2 TIMI 51 Phase III clinical trial in 15,526 patients was the basis for the 2013 EMA approval of low-dose rivaroxaban (2.5 mg twice-daily) added to standard antiplatelet therapy (aspirin alone or aspirin plus clopidogrel or ticlopidine) in patients with a recent ACS with elevated cardiac biomarkers.<sup>14</sup> This trial evaluated two different low-dose rivaroxaban treatment strategies (2.5 mg and 5 mg twice-daily) on top of antiplatelet therapy (either aspirin alone or aspirin and clopidogrel or ticlopidine) in comparison to placebo on top of antiplatelet therapy. The 2.5 mg twice-daily dose was associated with a significant reduction of the combined primary efficacy endpoint of cardiovascular death, myocardial infarction or stroke (9.1% versus 10.7% for rivaroxaban versus placebo, respectively,  $p=0.02$ ). Furthermore, rivaroxaban 2.5 mg twice-daily also significantly reduced cardiovascular and all-cause death (2.7% versus 4.1% and 2.9% versus 4.5%,

respectively, both  $p=0.002$ ), while increasing the risk for thrombolysis in myocardial infarction (TIMI) major bleeding events not associated with coronary artery bypass grafting (1.8% versus 0.6%,  $p<0.001$ )<sup>14</sup> and of intracranial haemorrhage (0.4% versus 0.2%,  $p=0.04$ ). But importantly it did not increase the rates of fatal bleeding (0.1% versus 0.2%,  $p=0.45$ ) or fatal intracranial haemorrhage (0.1% versus 0.1%).<sup>15</sup>

The low-dose rivaroxaban therapy did significantly reduce cardiovascular death in patients with ACS when it was co-administered with standard platelet therapy consisting of low-dose aspirin alone or in combination with clopidogrel or ticlopidine in ATLAS ACS 2 TIMI 51.<sup>14</sup> Patients included in this trial had a mean age of 62 years, which is younger than the typical patient requiring oral anticoagulation for atrial fibrillation and therefore would have a lower risk for bleeding events compared to patients that were exposed to higher doses of rivaroxaban in the ROCKET AF trial. Furthermore, these patients were not treated with third generation P2Y12 inhibitors (prasugrel or ticagrelor), which are known to be associated with a higher rate of bleeding events compared to clopidogrel.<sup>16,17</sup> Therefore, the significance of a long-term attenuation of the coagulation system with the direct factor Xa inhibitor rivaroxaban after a recent ACS remains to be determined in the current clinical setting of antithrombotic therapy with a low-dose. It also remains to be examined whether a reduction from dual to single antiplatelet therapy in combination with low-dose factor Xa inhibition could provide an even better protection from ischaemic cardiovascular events, without a substantial increase in bleeding risk. This potentially paradigm-shifting novel strategy in antithrombotic therapy in ACS would need to be explored by future clinical trials.

## PATIENT CONSIDERATIONS

While elderly patients with atrial fibrillation do have a higher risk for systemic thromboembolism and stroke, they also exhibit a higher risk for major bleeding events. Recent meta-analyses including major clinical trials with the novel oral anticoagulant rivaroxaban conclude that the beneficial effects of anticoagulation are preserved in the elderly population.<sup>18,19</sup> However, reductions in daily dosing may be necessary based on the individual bleeding risk of the elderly



patient, including regular assessment of renal function.<sup>18,19</sup> There is currently no special dosing recommendation for obese patients. In a study with healthy obese subjects with a bodyweight >120kg, the maximum plasma concentration of a fixed dose of rivaroxaban was unaffected.<sup>20</sup>

When interruption of anticoagulation with rivaroxaban is necessary due to surgical procedures, it is recommended to stop rivaroxaban intake at least 24 hours prior to surgery.<sup>21</sup> Depending on the balance of the bleeding risk associated with the surgical procedure and on the individual risk for thromboembolic complications without anticoagulation, it may be deemed necessary to withhold rivaroxaban for 48 hours before the surgical procedure.<sup>22</sup> There is broad agreement that, due to the pharmacology of the novel oral anticoagulants, there is no need for a bridging therapy with parenteral anticoagulants when oral anticoagulation needs to be interrupted for planned surgical procedures.<sup>21,22</sup>

## SUMMARY AND CONCLUSION

The direct oral factor Xa inhibitor rivaroxaban is currently the compound with the widest clinical approval within the group of the oral direct factor Xa inhibitors. It was the first oral factor Xa inhibitor to gain clinical approval in 2008 for the prevention of VTE after elective hip or knee

replacement surgery, and also the first with clinical approval for long-term oral anticoagulation for stroke prevention in patients with non-valvular AF in 2011. Since then, rivaroxaban was also approved for the treatment and secondary prevention of DVT and PE, and just recently a low-dose rivaroxaban has gained approval when added to standard antiplatelet therapy in patients after an ACS with elevated cardiac biomarkers. Across the clinical indications, AF, DVT and PE, oral anticoagulation with rivaroxaban demonstrated non-inferior efficacy as compared with dose-adjusted vitamin-K-antagonist.

The dosing of rivaroxaban for oral anticoagulation is without the need for routine measurements of coagulation parameters. With the exception of the first 3 weeks after an acute PE or DVT, where rivaroxaban is given twice-daily at a dose of 15 mg, rivaroxaban is used at a once-daily dose of 20 mg for treatment and secondary prevention of DVT and PE, and for stroke prevention in AF (15 mg if creatinine clearance is 15-49 ml/min). For prevention of VTE after elective hip or knee replacement, a once-daily dose of 10 mg is administered. The role of the recently EMA-approved low-dose rivaroxaban therapy (2.5 mg twice-daily) in combination with aspirin and clopidogrel or ticlopidine after ACS, still needs to be determined in the current setting of the wide clinical usage of the third generation P2Y<sub>12</sub> inhibitors prasugrel and ticagrelor.

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