

# Role of rivaroxaban in the management of atrial fibrillation: insights from clinical practice

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**Abstract:** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and it leads to significant morbidity and mortality, predominantly from ischemic stroke. Vitamin K antagonists, mainly warfarin, have been used for decades to prevent ischemic stroke in AF, but their use is limited due to interactions with food and other drugs, as well as the requirement for regular monitoring of the international normalized ratio. Rivaroxaban, a direct factor Xa inhibitor and the most commonly used non-vitamin K oral anticoagulant, avoids many of these challenges and is being prescribed with increasing frequency for stroke prevention in non-valvular AF. Randomized controlled trial (RCT) data from the ROCKET-AF (Rivaroxaban once daily oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) trial have shown rivaroxaban to be non-inferior to warfarin in preventing ischemic stroke and systemic embolism and to have comparable overall bleeding rates. Applicability of the RCT data to real-world practice can sometimes be limited by complex clinical scenarios or multiple comorbidities not adequately represented in the trials. Available real-world evidence in non-valvular AF patients with comorbidities – including renal impairment, acute coronary syndrome, diabetes mellitus, malignancy, or old age – supports the use of rivaroxaban as safe and effective in preventing ischemic stroke in these subgroups, though with some important considerations required to reduce bleeding risk. Patient perspectives on rivaroxaban use are also considered. Real-world evidence indicates superior rates of drug adherence with rivaroxaban when compared with vitamin K antagonists and with alternative non-vitamin K oral anticoagulants – perhaps, in part, due to its once-daily dosing regimen. Furthermore, self-reported quality of life scores are highest among patients compliant with rivaroxaban therapy. The generally high levels of patient satisfaction with rivaroxaban therapy contribute to overall favorable clinical outcomes.

**Keywords:** rivaroxaban, atrial fibrillation, anticoagulation, thromboembolism, adherence

## Introduction

Atrial fibrillation (AF) remains the most frequent sustained cardiac arrhythmia<sup>1</sup> causing significant morbidity and mortality, and estimates suggest that its prevalence is increasing.<sup>1</sup> AF is a chronic disorder that results in left atrial stasis and is thus associated with an increased risk of left atrial thrombus formation, and subsequent embolization to the brain causing stroke or systemic arterial thromboembolism. The main aims of the treatment for AF are the prevention of thromboembolic complications, such as stroke or systemic embolism (SE), and alleviation of symptoms.<sup>2</sup> Current guidelines<sup>3</sup> recommend that care of patients with AF should take into account individual needs and preferences, with physicians offering patients a personalized package of care.

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This includes a risk-based approach to stroke prevention and discussion of options for thromboprophylaxis.<sup>4</sup>

Historically, vitamin K antagonists (VKAs), mainly warfarin, were the only available oral anticoagulants (OACs) for patients with AF. However, the narrow therapeutic window, which necessitates regular monitoring and dose adjustment, as well as the interactions with food, alcohol, and other drug–drug interactions limit the use of VKAs.<sup>4–6</sup> Coagulation monitoring using the international normalized ratio (INR) is required,<sup>4,6</sup> which has been the cornerstone of effective management of patients treated with VKA.

Non-vitamin K oral anticoagulants (NOACs), including factor Xa inhibitors rivaroxaban (Bayer AG, Leverkusen, Germany), apixaban (Bristol-Myers Squibb Co., New York City, NY, USA), and edoxaban (Daiichi Sankyo, Tokyo, Japan) and the direct thrombin inhibitor dabigatran, provide predictable pharmacological effects (onset and offset) that negate the need for monitoring,<sup>3,4</sup> making this class of drugs a very attractive alternative to VKA. Since their introduction in the UK in 2008 (initially for thromboprophylaxis of deep venous thrombosis), prescriptions for NOACs have increased significantly, so that they now account for the majority of OAC prescriptions. In 2015, NOACs accounted for 56.5% of all OAC prescriptions, with rivaroxaban being the most frequently prescribed, followed by apixaban and dabigatran.<sup>7,8</sup>

## Mode of action of rivaroxaban

Rivaroxaban is a direct oral factor Xa inhibitor. Factor Xa is produced via the intrinsic and extrinsic coagulation pathways and is the rate-limiting step in the propagation of thrombin generation. Indeed, factor Xa may be a better target than thrombin because it has fewer functions outside coagulation; thus, inhibition of factor Xa may cause fewer side effects.<sup>4</sup> Rivaroxaban acts as an anticoagulant by selectively, directly, and reversibly inhibiting free and clot-associated factor Xa in human plasma without binding to antithrombin.<sup>8,9</sup> This results in the inhibition of the conversion of factor II (prothrombin) to factor IIa (thrombin). Rivaroxaban is 100,000-fold more selective for factor Xa than other biological proteases, such as thrombin, plasmin, factor VIIa, factor IXa, and activated protein C<sup>8,10</sup> with no direct effect on platelet aggregation. Rivaroxaban is well tolerated, with a predictable pharmacokinetic profile, without the need for laboratory monitoring.<sup>8</sup>

## Pharmacodynamics

Rivaroxaban is well tolerated in healthy human subjects, with rapid onset of action and dose-proportional pharmacodynamics and pharmacokinetics. Studies published more than a decade ago demonstrate that 20%–61% of inhibition of factor

Xa occurs with rivaroxaban at doses of 5–80 mg. Maximum inhibition was seen to occur 1–4 hours after administration, and these effects lasted 5–12 hours.<sup>8,9,11</sup> Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) were also observed to be prolonged in a dose-dependent manner.<sup>8,11</sup> The respective prolongation of PT was 1.3–2.6 times the baseline value<sup>8,10</sup> and around 1.5 times from baseline<sup>8,11</sup> for aPTT. These values were achieved within 1–4 hours after administration of rivaroxaban.<sup>8,9</sup>

## Pharmacokinetics

After oral administration, rivaroxaban is absorbed rapidly and almost completely. Peak plasma concentrations ( $C_{max}$ ) are attained, and bioavailability is 80%–100% with the 10 mg tablet dose.<sup>8,9,11,12</sup> Area under the curve (AUC) was not affected by food intake at this dose.<sup>13</sup> Nevertheless, the rate of absorption and bioavailability of a 20 mg tablet appears to decline without food. However, under fed conditions, there is a resultant increase in rivaroxaban concentration.<sup>13</sup> The pharmacokinetics of rivaroxaban do not appear to be affected by the type of food consumed.<sup>13</sup> Approximately 90% of rivaroxaban is protein bound and its volume of distribution is about 1.36 L/kg.<sup>8,10</sup> Rivaroxaban has no major active circulation metabolites and is metabolized in the liver by cytochrome P450 isoenzyme 3A4. It has a dual-mode excretion process via renal elimination and a small amount via the fecal and biliary routes. Approximately 14%–31% of the drug is excreted unchanged in the urine.<sup>8,10,12</sup> Rivaroxaban's elimination half-life, at doses ranging from 5 mg daily to 30 mg twice daily, is 5–9 hours.<sup>8,9,12</sup> When administered to patients >75 years of age, patients with renal insufficiency (a creatinine clearance below 50 mL/minute), patients with low body weight (<50 kg), and patients with moderate hepatic disease (Child-Pugh class B), rivaroxaban was associated with reduced renal clearance, a higher (AUC) concentration, and increased factor Xa inhibition, indicating that dosage adjustments might be necessary for these patients.<sup>8,10,12,14</sup>

## Real-world data on efficacy and safety in different patient groups

### Overall efficacy and safety

The effectiveness of rivaroxaban in non-valvular AF (NVAf) was first shown in the ROCKET-AF (Rivaroxaban once daily oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) trial,<sup>15</sup> a large, multi-center, randomized, double-blind trial with 14,264 patients. Rivaroxaban was non-inferior to warfarin in preventing ischemic stroke and SE. Overall rates of major and clinically relevant non-major

bleeds were no different between the two groups, but there were more gastrointestinal bleeds in the rivaroxaban group than in the warfarin group (3.2% vs 2.2%,  $p < 0.001$ ). There were, however, significantly fewer intracranial or fatal bleeds in the rivaroxaban group than in the warfarin group (0.5% vs 0.7% per year, HR 0.67, 95% CI: 0.47–0.93,  $p = 0.02$ ).

Randomized controlled trials (RCTs), the gold standard for assessing the efficacy and safety of a drug or intervention, have a strict set of inclusion and exclusion criteria and use specific protocols for the treatment and follow-up of the patients involved.<sup>16</sup> While this has obvious advantages when the efficacy and safety of a drug is being investigated, real-life patients outside of clinical trials may be more complex than those participating in RCTs. Patients who would have been excluded due to frailty, bleeding risk, or specific comorbidities may nevertheless have a clear indication for anticoagulation. When newly licensed drugs are used in day-to-day practice, their efficacy and safety profile may be seen through observational studies, which can complement the findings of RCTs.<sup>17</sup>

The first such study to assess the effectiveness of rivaroxaban for stroke prevention in AF in the real-world setting was XANTUS (Xarelto® on prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation).<sup>18</sup> The population of 6,784 patients in XANTUS was at a lower risk of stroke, with a mean CHADS<sub>2</sub> score of 2.0 compared with a CHADS<sub>2</sub> score of 3.5 in ROCKET-AF, and only 19% of patients had previously suffered a stroke, transient ischemic attack (TIA), or SE compared with 55% in ROCKET-AF. Fatal bleeding events were seen to occur at a rate of 0.2 per 100 patient-years, intracranial hemorrhage at a rate of 0.4 events per 100 patient-years, and major gastrointestinal bleeding events at 0.9 events per 100 patient-years. Strokes occurred at a rate of 0.7 events per 100 patient-years (43 strokes in all, of which 32 were ischemic). In addition, a further eight patients experienced a systemic embolic event (0.1 events per 100 patient-years). In summary, the rates of both bleeding complications and thromboembolic events were found to be low in real-life clinical practice amongst patients treated with rivaroxaban.<sup>18</sup>

A recent systematic review and meta-analysis<sup>17</sup> of rivaroxaban use compared with dabigatran or warfarin in 17 real-world studies of stroke prophylaxis in NVAf found that the effectiveness of rivaroxaban was similar to that of dabigatran in preventing stroke or systemic thromboembolism (HR 1.02; 95% CI: 0.91–1.13) though with higher major bleeding (HR 1.38; 95% CI: 1.27–1.49) and GI bleeding (HR 1.33; 95%

CI: 1.18–1.48). Rates of acute myocardial infarction and intracerebral hemorrhage were comparable. Rivaroxaban was more effective than warfarin in reducing the rate of stroke or systemic thromboembolism (HR 0.75; 95% CI: 0.64–0.84). As was seen in the ROCKET trial, there were more GI bleeds in the rivaroxaban group (HR 1.2; 95% CI: 1.07–1.33) and fewer intracerebral bleeds (HR 0.54; 95% CI: 0.43–0.64). There was no significant difference in all-cause mortality.<sup>17</sup>

Real-world studies, such as registries and database analyses, can provide helpful evidence to aid management decisions where RCT data may be lacking. Data from such databases have recently been published, including the Dresden NOAC registry, which supports the short-term peri-procedural interruption of NOAC therapy as safe. Interestingly, in this same registry, analysis of patients who sustained a major bleeding event on an NOAC indicated that those patients who later recommenced OAC therapy, either with an NOAC or a VKA, had significantly lower mortality and a lower rate of recurrent major bleeding or thromboembolism than those who remained off OAC therapy. Real-world studies such as these can serve to complement the data available from RCTs, and inform decision making, including in complicated clinical scenarios.<sup>19</sup>

The XANTUS population generally had fewer comorbidities than were seen in the ROCKET-AF trial. Subgroup analyses from ROCKET-AF have shown broad consistency in efficacy and safety across a range of different patient groups. However, special considerations are appropriate when prescribing rivaroxaban in some patient groups due to the greater risk of bleeding complications. These are discussed below.

## Renal impairment

Patients with AF and renal disease are at a greater risk of both cerebrovascular ischemic events and bleeding events than those without renal impairment. At the milder end of the renal dysfunction spectrum, the trend is toward a greater risk of ischemic events,<sup>20</sup> whereas those with severe or end-stage renal disease are more prone to hemorrhage, predominantly due to platelet dysfunction.<sup>21</sup>

Furthermore, since one-third of the administered rivaroxaban dose is excreted via the kidneys, dose reduction is required if there is renal dysfunction (creatinine clearance 15–49 mL/minute), to avoid high plasma levels.<sup>22</sup> These patients should be prescribed 15 mg once per day, instead of the 20 mg once per day dose for those with preserved renal function (creatinine clearance  $\geq 50$  mL/minute). Rivaroxaban should be avoided altogether in end-stage renal disease (creatinine clearance  $< 15$  mL/minute).

It is not uncommon for patients to be prescribed or left on an inappropriately high or low dose of rivaroxaban for their level of renal function, and where dose reduction is not undertaken in renal dysfunction, there is an excess of major bleeding complications. By the same token, those prescribed a renal dose despite normal renal function are at an increased risk of stroke.<sup>23</sup> To ensure that patients are commenced and remain on the correct dose of rivaroxaban, renal function should be checked at baseline, annually thereafter, and in circumstances where there may be deterioration in renal function, such as with infection, dehydration, or surgery.<sup>24</sup>

Though end-stage renal disease is a contraindication to rivaroxaban use, its safety and efficacy in mild or moderate renal impairment is supported by a recent meta-analysis, in which NOAC therapy was compared to warfarin in this patient population. Ischemic stroke rates were found to be lower with NOACs in patients with mild renal impairment (relative risk [RR] 0.79; 95% CI: 0.68–0.91) and moderate renal impairment (RR 0.80; CI: 0.69–0.92). Major bleeding rates were also lower in mild (RR 0.86; CI: 0.77–0.95) and moderate renal impairment (RR 0.73; CI: 0.65–0.82).<sup>25</sup>

In another recent study, rivaroxaban, in particular, was shown to have a favorable risk profile in patients with renal dysfunction, with lower rates of eGFR deterioration, doubling of serum creatinine, and acute kidney injury episodes than were observed with warfarin. Other NOACs also compared favorably with warfarin, though not to the same extent.<sup>26</sup>

## Elderly patients

The prevalence of AF increases with age, and it is estimated to affect at least 10% of those over the age of 75 years.<sup>27</sup> Concern over bleeding complications has led to the underuse of anticoagulation in the elderly, leaving them at a greater risk of disabling ischemic stroke. Although the elderly are also at an increased risk of hemorrhage with oral anticoagulation, the benefit of ischemic stroke reduction exceeds the risk of hemorrhage for most patients.<sup>28</sup> The median age of patients in the ROCKET-AF trial was 73 years (interquartile range 65–78 years),<sup>28</sup> and the mean age in XANTUS was 71.5 years, with 37% of patients being >75 years old.<sup>28</sup> The safe and effective use of rivaroxaban in the elderly is well supported by available data, but care must be taken to address comorbidities that may increase the likelihood of bleeding complications and which are more prevalent in the older population, such as the risk of falls, renal dysfunction requiring dose reduction, and adequate control of hypertension.

## Acute coronary syndrome and percutaneous coronary intervention

Around 15% of patients with pre-existing AF also have an acute coronary syndrome (ACS) event.<sup>29</sup> Though both pathologies involve thrombosis, their pharmacological management differs. As a means of preventing ischemic stroke, OAC is superior to dual antiplatelet therapy (a combination of aspirin plus one of clopidogrel, ticagrelor, or prasugrel).<sup>30</sup> Meanwhile, dual antiplatelet therapy is superior to OAC with warfarin for preventing stent thrombosis in patients with ACS.<sup>31</sup> Those with concomitant AF and ACS may therefore have an indication for both dual antiplatelet therapy and OAC – so-called triple therapy.

The bleeding risk with triple therapy is not inconsiderable, particularly when used for prolonged periods, with one meta-analysis involving a total of 1,349 patients indicating a 2.2% 30-day risk of major bleeding rising to 12% at 1 year,<sup>32</sup> highlighting the need to minimize the duration of triple therapy to keep the risk–benefit balance favorable.

The 2016 European Society of Cardiology (ESC) Guidelines for the Management of Atrial Fibrillation<sup>3,33</sup> recommend that in patients with ACS and AF at low bleeding risk (HAS BLED  $\leq 2$ ), initial triple therapy comprising an NOAC and aspirin (75–100 mg/day) and clopidogrel (75 mg/day) should be considered for 6 months, irrespective of stent type (bare metal stent or drug-eluting stent), followed by (N)OAC and aspirin (75–100 mg/day) or clopidogrel (75 mg/day) continued up to 12 months. Furthermore, in patients requiring OAC at high bleeding risk (HAS BLED  $\geq 3$ ), triple therapy of (N)OAC and aspirin (75–100 mg/day) and clopidogrel (75 mg/day) should be considered for a duration of 1 month followed by (N)OAC and aspirin (75–100 mg/day) or clopidogrel (75 mg/day) irrespective of clinical setting and stent type until 12 months post ACS. These guidelines are supported by the recent 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.<sup>34</sup>

The recent PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial<sup>35</sup> randomized 2,124 patients with NVAF who had undergone percutaneous coronary intervention (PCI) to one of three groups. Group 1 received rivaroxaban 15 mg once daily with a P2Y<sub>12</sub> inhibitor (clopidogrel or ticagrelor) for a total of 12 months, group 2 were given rivaroxaban 2.5 mg b.i.d. with dual antiplatelet therapy for 1, 6, or 12 months, and group 3 were given a VKA plus dual antiplatelet therapy for 1, 6, or 12 months.

There was a significantly reduced rate of bleeding complications, including major, minor, or other bleeds requiring medical attention, in the two rivaroxaban groups compared with VKA group (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3). There was no significant difference seen in cardiovascular mortality between the groups or in the rates of stroke. In fact, the study was not sufficiently powered to find a difference in rates of strokes. With safety having been established, further work is needed to determine adequate efficacy as far as stroke prevention is concerned.<sup>35</sup>

Four other trials in this patient population are currently ongoing: RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting),<sup>36</sup> AUGUSTUS (A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis [Blood Clots] Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart), SAFE-A (Rationale and design of the SAFE-A study: SAFety and Effectiveness trial of Apixaban use in association with dual antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention), and ENTRUST-AF PCI (Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement). These trials will aim to determine the efficacy and safety of three other NOACs in combination with antiplatelet therapy compared with warfarin and antiplatelet therapy. RE-DUAL PCI will compare dabigatran plus P2Y<sub>12</sub> inhibitor therapy to triple therapy with warfarin, aspirin, and a P2Y<sub>12</sub> inhibitor.<sup>36</sup> The AUGUSTUS trial will compare apixaban plus a P2Y<sub>12</sub> inhibitor with or without aspirin, with warfarin plus P2Y<sub>12</sub> inhibitor with or without aspirin (<https://clinicaltrials.gov/ct2/show/NCT02415400>). The SAFE-A trial will be comparing 1 month vs 6 months of triple therapy comprising apixaban plus P2Y<sub>12</sub> inhibitor plus aspirin after drug-eluting stent implantation in patients with NVAF.<sup>37</sup> The ENTRUST-AF PCI trial will compare the combination of edoxaban plus P2Y<sub>12</sub> inhibitor against the combination of warfarin, aspirin, and a P2Y<sub>12</sub> inhibitor in patients with AF undergoing PCI.<sup>38</sup> Hopefully, these trials will provide further useful data to enable informed clinical decision making in this important patient population.

## Diabetes mellitus

Diabetes and AF often coexist, and diabetes itself is a significant risk factor for ischemic stroke. Longer duration of

diabetes is associated with a higher risk of ischemic stroke, while the degree of strict glycemic control does not appear to be as important.<sup>39</sup> Diabetes alone, without coexisting renal dysfunction, does not increase the risk of bleeding complications from OAC therapy, and German registry data indicate that diabetes is one of the several risk factors for the discontinuation of rivaroxaban therapy (HR 1.39; 95% CI: 1.06–1.82;  $p=0.018$ ).<sup>40</sup> Given the greater risk of ischemic stroke without an increase in bleeding risk from rivaroxaban therapy, it may be appropriate to give special attention to address any concerns that may limit adherence in such patients. An on-going post-marketing safety surveillance observational study in nearly 45,000 people with NVAF found that the incidence of major bleeding in diabetics was generally consistent with reports from the ROCKET AF subgroup analysis.<sup>41</sup>

## Malignancy

Active cancer is a hypercoagulable state, which confers an increased risk of ischemic stroke, but there may also be a greater risk of bleeding events with local tumor invasion. Where such patients also have AF, decisions on anticoagulation can prove challenging.<sup>42</sup> Patients with serious concomitant illness associated with a life expectancy of <2 years were excluded from ROCKET-AF, although rivaroxaban has been shown in other studies to have satisfactory safety and efficacy for treating venous thromboembolic disease in the context of malignancy.<sup>43</sup>

A recent registry of 163 patients with NVAF and active malignancy receiving rivaroxaban showed similar safety and efficacy for rivaroxaban as that shown in ROCKET-AF, albeit in a much smaller cohort of patients.<sup>42</sup> After adjustment for risk factors, in this population with active malignancy with some 59% of patients with stage IV disease, the cumulative incidence of stroke at 1 year was 1.4%, major bleeding was 1.2%, clinically relevant non-major bleeding was 14%, and death was 22.6%.<sup>42</sup> The risk of clinically relevant non-major bleeding, leading to discontinuation of anticoagulation at 1 year was 14.0% (95% CI: 4.2–22.7%). The data available are limited, but indicate that rivaroxaban can be considered for NVAF patients with cancer.

## Patient-focused perspectives Adherence

The degree to which a prescribed drug is taken as intended by the prescribing clinician has a significant impact on both efficacy and safety, and adherence is frequently poor with cardiovascular medicines of any kind and among all patient

groups.<sup>44</sup> Common reasons for this include often complicated dosing regimens, large pill size, fear of side effects, forgetfulness, and a lack of understanding of the intended benefits.<sup>45</sup>

For some, the additional specific inconveniences associated with VKA such as warfarin – having to undergo regular blood tests, attend anticoagulation clinic appointments, avoid specific foods and their interactions with alcohol, drug interactions – also contribute to poor adherence.<sup>45</sup> The inevitable consequence of poor adherence to the prescribed regimen is suboptimal time in therapeutic range (TTR), which carries with it an excess risk of thromboembolic events and bleeding.<sup>46</sup> Even with regular INR monitoring, TTR is still low in a significant proportion of patients, and up to three quarters of patients taking warfarin for AF who present with an ischemic stroke have a subtherapeutic INR at the time of the event.<sup>47</sup>

The advent of NOACs has removed some of the challenges associated with VKAs, including the need for regular blood test monitoring. NOACs have the advantage of being given in a fixed dosing regimen, for example, rivaroxaban 20 mg once daily for patients with creatinine clearance >50 mL/minute, or a reduced dose of 15 mg once daily in patients with creatinine clearance 15–50 mL/minute.

Therefore, as might be expected, adherence to OAC is better in patients taking NOACs than that in patients on a VKA. An Australian study of 2,819 patients with NVAf (1,471 taking NOACs – 15% apixaban, 44% dabigatran, 41% rivaroxaban – and 1,348 taking warfarin), looked at the proportion of patients not filling a first repeat prescription and discontinuing the treatment within 12 months.<sup>48</sup> In the NOAC group, 9% failed to fill a first repeat prescription and 30% discontinued within 12 months compared with 14% and 62%, respectively, in the warfarin group. Regression analysis adjusted for age, sex, heart failure, diabetes, and hypertension, showed that overall, patients on warfarin were 2.5 times more likely to stop taking their prescribed anticoagulant than were patients on an NOAC (HR 2.47, 95% CI: 2.19–2.79).<sup>48</sup> Danish experience shows a similar story. Registry data from 46,675 patients with NVAf were used to compare adherence with VKA to that seen with NOACs. Accordingly, 57.3% of patients were taking a VKA, 29.8% dabigatran, 8.5% rivaroxaban, and 4.4% apixaban.<sup>49</sup> The highest levels of adherence, as measured by the Proportions of Days Covered (PDC) >80%, were seen in patients taking rivaroxaban. In comparison with rivaroxaban, the odds ratio for a PDC >80% for apixaban was 0.79 (95% CI: 0.69–0.92), for dabigatran was 0.72 (95% CI: 0.66–0.80), and for VKA was 0.76 (95% CI: 0.69–0.83). Again, using rivaroxaban as a reference, the hazard ratio for repeat prescription gaps

of between 7 and 89 days for apixaban, was 1.52 (95% CI: 1.36–1.69), for dabigatran, 1.72 (95% CI: 1.60–1.85), and for VKA, 2.36 (95% CI: 2.20–2.52). Furthermore, in 11.5% of patients taking VKA, refill gaps of longer than 89 days were seen.<sup>49</sup>

Adherence to rivaroxaban also compares favorably with that seen with other NOACs. A study of 14,469 patients with NVAf, comparing adherence with once-daily rivaroxaban (11,477 patients) and twice-daily apixaban (2,992 patients) at 90 and 180 days, found that rivaroxaban users had a higher PDC >80% than apixaban users at 90 days (85.3% vs 79.9%,  $p<0.001$ ) and at 180 days (75.8% vs 72.2%,  $p=0.001$ ). Repeat prescription gaps of at least 5 and 10 days were also lower in the rivaroxaban group than in the apixaban group (54.2% vs 62.4% [ $p<0.001$ ], and 40% vs 49.2% [ $p<0.001$ ] respectively).<sup>50</sup> Similar findings have been reported in comparisons of rivaroxaban with dabigatran, another twice-daily NOAC.<sup>51,52</sup> It may be seen that adherence to NOAC therapy is imperfect, but significantly better than with warfarin, and between NOACs – significantly better with the once-a-day rivaroxaban.

## Once-daily dosing

The once-daily dosing regimen with rivaroxaban has significant advantages over twice a day regimens. A patient's understanding of dosing instructions is fundamental to the drug being taken as intended and is understandably greater with simpler dosing regimens. Understanding of dosing instructions and compliance are reduced both with more complex dosing regimens and with an increasing number of other medications being taken.<sup>53</sup>

Furthermore, patients taking twice-daily drugs often do not space them out at the desired 12-hour dosing intervals, with intervals in practice ranging between as little as 1 hour and as many as 18 hours.<sup>54</sup> This can lead to greater variability in drug plasma concentrations and the potential to leave patients at a greater risk of either bleeding or thromboembolic events. On the other hand, this needs to be weighed up against the more forgiving pharmacokinetics of twice-daily drugs in the event of occasional doses being missed.<sup>55</sup>

Whichever anticoagulant is prescribed, improved adherence and better outcomes are seen in patients who are adequately involved in the decision-making process. The question of once-daily vs twice-daily dosing should be an important part of the discussion when conferring with patients about the anticoagulant they take.<sup>24</sup> The 2016 ESC<sup>3</sup> guidelines highlight the importance of patient education in empowering them to support the management of their AF.

## Satisfaction and quality of life

Closely tied to adherence levels is patient satisfaction with the prescribed medication, and its perceived impact on quality of life (QOL). SAFARI (Satisfaction/Quality of Life With Rivaroxaban in Stroke Prevention in Atrial Fibrillation Indication) is a French prospective, multicenter observational study of 405 patients with NVAF who switched from VKA to rivaroxaban, intended to show whether, in real-life practice, patient satisfaction is improved after making the change from VKA to rivaroxaban.<sup>56</sup> Patient satisfaction levels and QOL were assessed by means of the validated 15-item Anti-Clot Treatment Scale (ACTS) (including the 12-item ACTS Burden scale, and the 3-item ACTS Benefits scale, with higher numbers indicating greater levels of satisfaction) and the validated SF-36 health survey. Assessment was undertaken at baseline, 1, 3, and 6 months. There was an improvement in satisfaction, with baseline burden scores rising from a mean of 46.5 at baseline to 54.8 at 6 months ( $p<0.001$ ), and baseline benefit scores rising from a mean of 10.4 to 10.8 at 6 months ( $p=0.02$ ).<sup>56</sup> Statistical significance was reached, albeit with only a modest effect size. Slight improvements were seen in patients' QOL but did not reach statistical significance. A total of 106 treatment-related adverse events were experienced by 81 patients (19.7%), of which around half led to rivaroxaban discontinuation, the most common being gastrointestinal problems such as gingival and digestive bleeding. There were 11 serious bleeding events attributed to the rivaroxaban, including one death from hemorrhagic stroke.<sup>56</sup>

The much larger, international registry study, XANTUS, analyzed data from 1,291 patients with NVAF making the change from VKA to rivaroxaban.<sup>18</sup> The mean baseline ACTS burden score was  $50.51\pm 8.42$  and the mean benefit score was  $10.30\pm 2.70$ . Changes in these scores at 3-month follow-up were reported as least-squared mean differences and were improved by 4.38 points (95% CI: 2.53–6.22,  $p<0.0001$ ) for the ACTS burden score, and 1.01 points (95% CI: 0.27–1.75,  $p=0.0075$ ) for the benefit score.<sup>57</sup>

The Swiss STAR (Initiation of rivaroxaban in patients with non-valvular atrial fibrillation at the primary care level: the Swiss Therapy in Atrial Fibrillation for the Regulation of Coagulation) study of 537 patients with NVAF in the primary care setting also demonstrated improvements in patient satisfaction with treatment after commencement of rivaroxaban.<sup>58</sup> In this study, 56% of patients were switched from VKA to rivaroxaban (STR group), predominantly to avoid the need for routine INR monitoring, and 44% of patients were VKA naïve (VN group). Patient satisfaction was assessed on a 6-point scale with higher numbers indicating higher

satisfaction. In the STR group, it rose from  $3.6\pm 1.4$  on VKA therapy to  $5.5\pm 0.8$  on rivaroxaban at 3 months ( $p<0.001$ ). Such an improvement might be expected given that these patients had made the change to an NOAC in order not to have the inconvenience of regular blood tests, but a similar satisfaction level was also seen in the VN group:  $5.4\pm 0.9$ . Physician satisfaction was also assessed, and it improved from  $3.9\pm 1.3$  to  $5.4\pm 0.9$  in the STR group and was  $5.5\pm 0.7$  in the VN group. During the comparatively short follow-up period of 3 months, rivaroxaban was discontinued in 30 (5.6%) patients, predominantly due to side effects. There were 1 ischemic stroke, 2 major non-fatal bleeds, and 11 minor bleeds.<sup>58</sup>

QOL is closely associated with satisfaction and adherence, as found in a Spanish multicenter (including primary and secondary care centers), prospective study of 412 patients taking rivaroxaban for NVAF. At 6 months, there was no significant difference in QOL between the compliant and non-compliant groups, but after 12 months the difference was marked, with mean QOL scores of 124.67 (SD 30.78) in the non-compliant group and 83.47 (SD 26.44) in the compliant group ( $p<0.01$ ), with higher scores indicating a worse QOL. Other predictors of poor QOL found were polypharmacy, older age, previous treatment with a VKA, and comorbidities.<sup>59</sup>

## Conclusion

Symptom control and prevention of major complications such as thromboembolism are the two main aims of effective AF management. In preventing stroke and SE, both the ESC and National Institute of Clinical Excellence (NICE) guidelines recommend NOAC over VKA in patients with NVAF in whom anticoagulant therapy is indicated. Rivaroxaban is an NOAC approved for and indicated to reduce the risk of stroke and SE in patients with NVAF, and has been shown to be non-inferior in this regard to VKA. Rivaroxaban has been shown to be well tolerated with superior safety with regards to bleeding events compared with warfarin. Trial data from ROCKET-AF are supported by a huge wealth of data from post-marketing surveillance registries with rivaroxaban showing safety and efficacy, in line with what was seen in clinical trials. Such registries also provide important insights into the safety of rivaroxaban use in NVAF patients with comorbidities, including renal impairment, ACS, diabetes mellitus, malignancy, or old age. Post-marketing observational studies of rivaroxaban complement the outcomes of landmark trials through the use of unselected real-world populations and conditions and show that rivaroxaban use

in patients with NVAF is associated with a low risk of major bleeding and stroke.

## Disclosure

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