



# Continued commitment to safety: building on the existing rivaroxaban knowledge base

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Data from post-authorization studies and registries are valuable in establishing the safety and effectiveness of therapies in real-life settings, particularly as physicians may have concerns about the robustness of safety data from randomized controlled trials (RCTs). Furthermore, in routine clinical practice, there may be a potential for increased adverse event reporting with new therapies, and their true safety profile may be difficult to elucidate. The non-vitamin K antagonist (VKA) oral anticoagulant (NOAC) rivaroxaban is a direct factor Xa inhibitor, first approved for the prevention of venous thromboembolism (VTE) following elective hip or knee replacement surgery in 2008, and now licensed for use in five indications in Europe in the venous and arterial thromboembolic space. A number of Phase IV, non-interventional studies, and independent registries are completed or underway that aim to further evaluate safety outcomes with rivaroxaban in everyday clinical practice. These include XAMOS (Xarelto in the prophylaxis of post-surgical venous thromboembolism after elective Major Orthopaedic Surgery of the hip or knee), XANTUS (Xarelto on prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation), and XALIA (Xarelto for Long-term and Initial Anticoagulation in venous thromboembolism). Results to date—from XAMOS—show that rivaroxaban has an acceptable safety profile in real-life, with outcomes that are in line with the RECORD (REGulation of Coagulation in ORthopedic surgery to prevent Deep vein thrombosis and pulmonary embolism) clinical trial programme. International and national registries are also gathering information on rivaroxaban and other NOACs. Together, this breadth of studies illustrates an ongoing commitment to understanding real-life outcomes with NOACs.

## Introduction

Randomized controlled trials (RCTs) remain the ‘gold standard’ for assessing the efficacy and safety of new therapies. However, they have a number of limitations, including relatively small sample sizes, selective populations, short follow-up, the use of surrogate endpoints, and limited generalizability.<sup>1,2</sup> Following the drug approval process, concerns may remain regarding the safety of new

drugs in patients treated in everyday practice; there is a need to establish the safety and effectiveness of new therapies in real-life settings. For this reason, regulatory authorities may require post-authorization studies as a condition of the drug’s approval.

Such post-authorization studies must be transparent and all results, including raw data, must be publicly available. A number of websites exist that help to fulfil this requirement. Examples include the US National Institute of Health’s ‘ClinicalTrials.gov’—an international database of publicly and privately supported clinical studies—and ClinicalStudyDataRequest.com—a portal (funded by

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numerous pharmaceutical companies) through which researchers can access anonymized patient level data.<sup>3,4</sup> Independent websites run by pharmaceutical companies, such as Bayer HealthCare's Trial Finder,<sup>5</sup> also exist.

Furthermore, regulatory bodies themselves have initiatives to improve the transparency and independence of post-authorization studies. The European Medicines Agency (EMA) established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP<sup>®</sup>) in 2006. The network brings together academic and hospital-based research centres and facilitates the conduct of high-quality, multicentre, independent studies of medicines focusing on safety and benefit-risk profiles.<sup>6</sup>

'Post-authorization research' is a generic term used to describe all activities after drug approval by the regulatory agency. Post-authorization—or post-marketing—studies concentrate more (but not exclusively) on safety. The most commonly used approaches for monitoring drug safety are based on spontaneous reporting systems, automated linkage data, patient registries, case reports, and data obtained directly from a study.<sup>1</sup> Although reporting of adverse events to manufacturers is mandatory, late or non-reporting of cases to companies or regulators can be an issue. An analysis of adverse drug event monitoring at the US Food and Drug Administration (FDA) estimated that spontaneous reporting by practitioners captured just 1–13% of serious adverse events.<sup>7</sup> Conversely, one challenge with open-label observational studies is the potential for increased reporting of adverse events with the new therapy—the so-called Weber effect.<sup>8</sup> This may be the result of increased patient exposure and greater interest in the therapy; however, when physicians become familiar with the therapy and its adverse event profile, the rate of reported adverse events usually declines.<sup>8</sup>

Data from post-authorization studies investigate various aspects of drug use—they can confirm correct product use in the broader population, identify and quantify adverse event rates, evaluate disease outcomes, identify off-label use, monitor adherence to treatment guidelines, and understand use in a real-life setting. Non-interventional studies and registries have a pivotal role in confirming the safety and effectiveness of newly approved interventions across the wide range of patients treated in routine practice. In this review, we examine real-life experience with the oral direct factor Xa inhibitor, rivaroxaban, particularly focusing on its safety profile.

## Real-life experience with rivaroxaban

Rivaroxaban has been approved in different markets across the globe for up to five indications across seven distinct areas of use on the basis of results from comprehensive Phase III clinical trial programmes. As an extension to these, a number of Phase IV, non-interventional, real-life studies have been initiated to observe and further evaluate rivaroxaban in everyday clinical practice. These include XAMOS (Xarelto in the prophylaxis of post-surgical venous thromboembolism after elective Major Orthopaedic Surgery of the hip or knee), XANTUS (Xarelto on prevention of

sStroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation), and XALIA (Xarelto for Long-term and Initial Anticoagulation in venous thromboembolism).

## Industry-sponsored non-interventional studies of rivaroxaban

### Venous thromboembolism prevention after major orthopaedic surgery

Venous thromboembolism (VTE) is a frequent and potentially life-threatening complication of orthopaedic surgery.<sup>9</sup> Rivaroxaban demonstrated superior efficacy and a similar safety profile to enoxaparin for the prevention of VTE in the four randomized, Phase III RECORD (REGulation of Coagulation in ORthopedic surgery to prevent Deep vein thrombosis and pulmonary embolism) studies in patients undergoing elective hip or knee replacement surgery.<sup>10–13</sup>

The objective of XAMOS was to investigate the safety and effectiveness of rivaroxaban in patients undergoing major orthopaedic surgery of the hip or knee, compared with other standard of care (SOC) pharmacological thromboprophylaxis in routine clinical practice.<sup>14</sup> The study, which ran from 2009 to 2011, collected data on the incidence of adverse events (including symptomatic thromboembolic and bleeding events) in adult patients from 252 centres in 37 countries worldwide, who underwent elective hip or knee replacement surgery (or lower limb fracture surgery, where approved).<sup>15</sup> The attending physician determined the type, duration, and dose of drug.

Of the 17 701 patients enrolled, 8778 received rivaroxaban and 8635 received SOC, of whom 81.7% received low-molecular-weight heparin (LMWH).<sup>15</sup> Baseline patient demographics were similar for patients receiving rivaroxaban and SOC group, and were also similar to those patients who received rivaroxaban in the RECORD programme.<sup>16</sup>

Unselected patients receiving rivaroxaban in routine clinical practice had a significantly lower incidence of symptomatic VTE compared with the SOC group [0.65% vs. 1.02%; odds ratio (OR) 0.63; 95% confidence interval (95% CI) 0.45–0.89; safety population; *Table 1*].<sup>15</sup> These outcomes are consistent with those for symptomatic VTE in the RECORD1–4 pooled analysis [rivaroxaban: 0.57%; enoxaparin: 1.32%; hazard ratio [HR]: 0.42; 95% CI 0.29–0.63].<sup>16</sup>

The incidences of major bleeding events were also similar between XAMOS and the RECORD studies. In XAMOS, treatment-emergent major bleeding occurred in 0.40% of patients in the rivaroxaban group and 0.34% of patients in the SOC group (OR 1.19; 95% CI 0.73–1.95; safety population; *Table 1*).<sup>15</sup> In the RECORD1–4 pooled analysis, the incidence of treatment-emergent major bleeding was 0.39% for rivaroxaban and 0.21% for enoxaparin, with no statistical difference between regimens (OR 1.84 [0.94–3.62]).<sup>16</sup>

An analysis using the EMA definition of major bleeding in XAMOS showed a statistically significant increase in the rivaroxaban group in the propensity score-adjusted population (*Table 1*).<sup>15</sup> The main contributor to this difference was a higher incidence of bleeding leading to

**Table 1** Incidence of thromboembolic events, treatment-emergent bleeding events, and other treatment-emergent adverse events (safety and propensity score-adjusted safety populations) in the XAMOS study<sup>15</sup>

Outcome	Safety population			Adjusted safety population (propensity score)		
	Rivaroxaban (n = 8778)		SOC (n = 8635)	Rivaroxaban (n = 8548)		SOC (n = 7968)
	n	Incidence (%)	n	Incidence (%)	OR (95% CI)	Weighted OR (95% CI)
Symptomatic thromboembolic events	78	0.89	117	1.35	0.65 (0.49–0.87)	0.69 (0.56–0.85)
Symptomatic arterial thromboembolic events <sup>a</sup>	20	0.23	29	0.34	0.68 (0.38–1.20)	0.88 (0.57–1.35)
Symptomatic venous thromboembolic events	57	0.65	88	1.02	0.63 (0.45–0.89)	0.63 (0.49–0.81)
RECORD major bleeding	35	0.40	29	0.34	1.19 (0.73–1.95)	1.35 (0.94–1.93)
EMA major bleeding	149	1.70	124	1.44	1.19 (0.93–1.51)	1.21 (1.01–1.45)

SOC, standard of care; CI, confidence interval; EMA, European Medicines Agency; OR, odds ratio.

<sup>a</sup>Includes myocardial infarction, cerebrovascular accident, ischaemic stroke, paresis, transient ischaemic attack, renal infarct, and femoral artery embolism.

treatment cessation.<sup>15</sup> In the RECORD1–4 pooled analysis, the rates of any bleeding events leading to permanent discontinuation of the study drugs were generally comparable between the rivaroxaban and enoxaparin groups (0.76% vs. 0.58%).<sup>16</sup> Bleeding warranting treatment cessation is no longer considered by the EMA as a sole criterion for a major bleeding event because the decision for treatment cessation may be subjective and influenced by other factors besides the severity of bleeding.<sup>17</sup> This is particularly relevant for open-label studies where adverse effects are more likely to be reported with a new agent. In XAMOS, when bleeding leading to treatment cessation was excluded from the EMA definition, the incidence of major bleeding was 1.3% for both the rivaroxaban and the SOC groups.<sup>15</sup> The incidence of critical site bleeding events (intracranial, retroperitoneal, intraocular, and intraspinal/haemorrhagic puncture) was low and comparable between rivaroxaban and SOC (<0.1% in both groups).<sup>15</sup>

The propensity score design was used to balance observed covariates across treatment groups in XAMOS.<sup>14</sup> This minimized selection bias and allowed comparison of groups with similar key baseline covariates. The propensity score adjustment achieved a more balanced population for important covariates [such as history of previous thrombotic events, frailty, and atrial fibrillation (AF)] between the rivaroxaban and the SOC groups, compared with the safety population (unadjusted data). The incidences of symptomatic thromboembolic and bleeding events were similar between the safety population (i.e. crude incidences) and the propensity score-adjusted safety population (weighted incidences; *Table 1*).<sup>15</sup>

As a first for a NOAC, the Committee for Medicinal Products for Human Use (CHMP) of the EMA recognized the strength of real-life evidence by voting positively to include overall results of XAMOS in the rivaroxaban 10 mg EU Summary of Product Characteristics.<sup>18</sup> XAMOS was the first study to present real-life experience of the safety and effectiveness of rivaroxaban for the prevention of VTE after major orthopaedic surgery of the hip or knee, and confirmed the favourable benefit-risk profile of rivaroxaban seen in the RECORD programme.<sup>15</sup>

### Stroke prevention in atrial fibrillation

Several other non-interventional trials of rivaroxaban in routine clinical practice are ongoing. XANTUS (Clinicaltrials.gov identifier: NCT01606995) is a prospective, international, observational, post-authorization, non-interventional study designed to collect safety and efficacy data on the use of rivaroxaban for stroke prevention in AF in routine clinical practice.<sup>19</sup> The key goal is to determine whether the safety profile of rivaroxaban as established in 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) is also observed in routine clinical practice. The Phase III ROCKET AF trial showed that rivaroxaban was non-inferior to warfarin for the reduction of stroke or systemic embolism in patients with AF.<sup>20</sup> Compared with warfarin, rivaroxaban significantly reduced rates of intracranial and fatal haemorrhages, although not rates of bleeding overall.<sup>20</sup>

XANTUS is designed as a single-arm cohort study to minimize selection bias, and will enrol ~6000 patients (from Europe and Canada) with non-valvular AF and who were prescribed rivaroxaban, irrespective of their level of stroke risk. Overall duration of follow-up will be 1 year; the first patient was enrolled in June 2012 and the study is estimated to complete in July 2015. Similar studies [XANTUS-EL (Xarelto on prevention of stroke and non-central nervous system systemic symbolism in patients with non-valvular atrial fibrillation in EMEA and Latin America; Clinicaltrials.gov identifier: NCT01800006) and XANAP (Xarelto for prevention of stroke in patients with atrial fibrillation in Asia-Pacific; Clinicaltrials.gov identifier: NCT01750788)] are ongoing across the globe. Data from these studies will supplement those from ROCKET AF and provide practical information concerning the use of rivaroxaban for stroke prevention in non-valvular AF.

### Treatment and secondary prevention of deep vein thrombosis

The Phase III EINSTEIN programme of rivaroxaban for the treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) involved three individual studies for treatment of: acute, symptomatic DVT (EINSTEIN DVT); acute, symptomatic PE (EINSTEIN PE), and long-term anticoagulation for those in whom there was no clear decision about continuing or stopping treatment (EINSTEIN Extension).<sup>21,22</sup>

In EINSTEIN DVT, a single-drug approach with rivaroxaban was non-inferior to dual therapy with enoxaparin/vitamin K antagonist (VKA) for the reduction of recurrent VTE, showing a similar safety profile and a net clinical benefit in favour of rivaroxaban.<sup>21</sup> As the use of rivaroxaban for the treatment of DVT increases in clinical practice, it is vital to further understand its applications in everyday patient care. XALIA (Clinicaltrials.gov identifier: NCT01619007) is a multicentre, prospective, non-interventional, observational study investigating the effectiveness and safety of rivaroxaban compared with standard therapy in patients with DVT.<sup>23</sup> The study cohort will include ~5200 patients with objectively confirmed acute DVT who will be treated for a period of  $\geq 3$  months. The primary outcomes will be the incidence of treatment-emergent adverse events (namely major bleeding), symptomatic recurrent VTE, and all-cause mortality. Secondary safety outcomes include major cardiovascular events; patient-reported treatment satisfaction and adherence; healthcare resource utilization and reasons for drug switching or interruption of treatment and adverse events, including serious adverse events. The first patient was enrolled in June 2012, with results expected in March 2015. XALIA will follow an international cohort of patients in Europe and other countries, including Israel and Canada, and will provide important information on DVT treatment in a real-life setting.<sup>23</sup>

### Interventional studies of rivaroxaban: investigating additional medical needs in clinical practice

It is important to note that not all post-authorization studies are non-interventional. Indeed, there are several

completed or ongoing interventional rivaroxaban studies designed to address a range of additional needs:

- X-VERT (eXplore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with nonvalvular atrial fibrillation scheduled for cardioversion): a randomized, open-label trial of rivaroxaban compared with VKAs for prevention of cardiovascular events in subjects with non-valvular AF scheduled for cardioversion.<sup>24</sup> Findings from X-VERT showed that in patients undergoing cardioversion, rivaroxaban appeared to be an effective alternative to VKAs for the composite of stroke, transient ischaemic attack (TIA), peripheral embolism, myocardial infarction (MI), and cardiovascular (CV) death (0.51% vs. 1.02%, respectively; risk ratio [RR] 0.50; 95% CI 0.15–1.73) with a favourable safety profile. Outcomes were not influenced by the use of early or delayed cardioversion. Furthermore, rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs ( $P < 0.001$ ). Taken together, these findings have resulted in rivaroxaban receiving European regulatory approval for a label extension to include use in patients with non-valvular AF undergoing cardioversion.<sup>24</sup>
- VENTURE-AF (Randomized, open-label, active-controlled multi-centre study to evaluate the safety of Rivaroxaban and vitamin K antagonists in subjects undergoing catheter ablation for Atrial Fibrillation): a randomized, open-label trial investigating the safety of uninterrupted rivaroxaban compared with a VKA in patients with non-valvular AF who are scheduled to undergo catheter ablation.<sup>25</sup>
- X-TRA (Xarelto–Thrombus Accelerated resolution): an open-label, non-randomized study of rivaroxaban for resolution of left atrial/left atrial appendage (LA/LAA) thrombus in patients with non-valvular AF or atrial flutter.<sup>26</sup>
- X-PLOERER (prospective, multicentre, randomized, heparin-controlled dose-finding trial to evaluate the efficacy and safety of rivaroxaban, a direct factor Xa inhibitor, on the background of standard dual antiplatelet therapy to support elective percutaneous coronary intervention): a randomized, open-label trial of rivaroxaban in combination with standard dual antiplatelet therapy (aspirin plus clopidogrel or ticlopidine) compared with unfractionated heparin (UFH) during elective percutaneous coronary intervention (PCI).<sup>27</sup> Data in 107 patients have shown there were fewer thrombotic events and less bleeding complications in patients who received rivaroxaban compared with UFH, and that this is a feasible approach for patients undergoing PCI.<sup>27</sup>
- PIONEER AF-PCI (open-label, randomized, controlled, multicentre study exploring two treatment strategies of Rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in patients with Atrial Fibrillation who undergo Percutaneous Coronary Intervention): a randomized, open-label trial that will assess the safety of two rivaroxaban treatment strategies and a dose-adjusted VKA treatment strategy after PCI (with stent placement) in patients with AF.<sup>28</sup>



### Non-interventional registries

Another source of real-life data is registries, which can be independent (investigator-initiated) or industry-sponsored. Over the past two decades, several major medical registries have been launched across many therapy areas in which anticoagulant therapy is used, including stroke prevention in patients with AF, prevention of VTE, and the treatment and secondary prevention of DVT and PE.

Dresden NOAC is an ongoing prospective registry that evaluates the effectiveness, safety, and management of all NOACs for stroke prevention in AF and for the treatment and secondary prevention of VTE in Saxony, Germany. In one of the first subgroup analyses, the rates, management, and outcomes of rivaroxaban-related bleeding in unselected patients in daily care were assessed.<sup>29</sup> A total of 1776/2346 patients enrolled (75.7%) received rivaroxaban: 1200 (67.5%) for stroke prevention in AF and 575 (32.4%) for the treatment of VTE. In the valid-for-safety analysis, the rates of major bleeding with rivaroxaban therapy per 100 patient-years were 3.4 (95% CI 2.6–4.4) for all patients, 3.1 (95% CI 2.2–4.3) for patients with AF, and 4.1 (95% CI 2.5–6.4) for patients with VTE, with no statistical difference between the AF and VTE groups. Therefore, real-life incidences of bleeding with rivaroxaban therapy are at least comparable with those seen with VKAs, maybe even lower.<sup>29</sup>

During rivaroxaban exposure, a total of 1082 bleeding events occurred in 762 patients.<sup>29</sup> Regarding the pattern and distribution of bleeding events, the majority occurred spontaneously (71.5% of all non-major clinically relevant (NMCR) bleeding, and 71.2% of all major bleeding). A total of 15.7% of all bleeding events occurred after trauma and 6.9% occurred after surgical or interventional procedures. Of the 1082 events, the majority (58.9%) was classed as International Society on Thrombosis and Haemostasis (ISTH) minor bleeding; 35% as ISTH NMCR bleeding and 6.1% as major bleeding. Major bleeding could be treated conservatively in 62.1% of cases (no treatment or compression/tamponade/transfusion only), whereas surgical or interventional treatment was necessary in 37.9% of cases. A total of nine patients received fresh frozen plasma, prothrombin complex concentrates, or both. When bleeding leading to hospitalization was assessed (including the 66 cases of major bleeding and another 32 NMCR bleeding events requiring hospital treatment), case fatality rates were 5.1 and 6.3% at Day 30 and Day 90, respectively.<sup>29</sup> This compares favourably with VKAs, where case fatality rates as high as 14% for major bleeding have been reported.<sup>30</sup> Taken together, these data indicate that real-life incidences of major bleeding with rivaroxaban therapy may be lower and outcomes at least not worse than those reported for VKAs.<sup>29</sup> While bleeding complications with rivaroxaban may be frequent in clinical practice, most of these are usually minor and may not require any intervention. Most major bleeding events can be managed using conservative strategies, and the use of procoagulants may be rarely needed to reverse the effects of anticoagulation.<sup>29</sup>

The short half-lives and rapid onset and offset of action of NOACs mean that treatment can be interrupted without the need for heparin bridging. The Dresden NOAC

registry has given an insight into safety outcomes in patients who require interventional procedures.<sup>31</sup> An analysis of 595 patients receiving NOACs who underwent 863 procedures (15.6% minimal, 74.3% minor, 10.1% major) found that NOACs were continued in 21.7% of patients, temporarily interrupted without heparin in 48.6% and interrupted with heparin bridging in 29.8%. At 30 days, rates of major cardiovascular events and major bleeding complications were 1.0 and 1.2%, respectively. Heparin bridging did not reduce cardiovascular events, and led to significantly higher rates of major bleeding complications compared with no bridging.<sup>31</sup>

Another independent German registry is ORTHO-TEP—a large, single-centre, retrospective comparison of rivaroxaban with the previous SOC (e.g. LMWH or fondaparinux) in over 5000 unselected patients undergoing elective hip or knee replacement surgery at the University Hospital ‘Carl Gustav Carus’ in Dresden, Germany. Data from ORTHO-TEP have shown that, in this setting, rivaroxaban is an acceptable alternative to LMWH and fondaparinux in routine clinical practice, with a significantly lower incidence of symptomatic VTE and fewer severe or major bleeding events.<sup>32,33</sup>

Other ongoing registries that will provide information about real-life NOAC safety include GARFIELD (Global Anticoagulant Registry in the FIELD) AF—an observational, multicentre, prospective study of patients with newly diagnosed AF and one or more investigator-defined risk factors for stroke.<sup>34</sup> The aim is to recruit at least 55 000 patients, enrolled <6 weeks after AF diagnosis in five independent, sequential cohorts and a retrospective cohort of 5000 patients with established AF.<sup>34</sup> GARFIELD VTE has an estimated recruitment of 10 000 patients in two sequential cohorts and will describe real-life outcomes in patients receiving treatment for DVT and/or PE (Clinicaltrials.gov identifier: NCT02155491). ORBIT-AF-II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) is a prospective outpatient registry involving 15 000 patients newly diagnosed with AF, as well as those with AF who have been recently started on a NOAC, and is currently recruiting in the USA and Puerto Rico. The primary aim of ORBIT-AF-II is to evaluate the safety and effectiveness of NOACs, with a focus on use, transitions and management around invasive procedures and bleeding events.<sup>35</sup> GLORIA-AF (GLObal Registry on long-term oral Antithrombotic treatment in patients with Atrial Fibrillation) is an international observational registry of 56 000 patents with non-valvular AF in 50 countries that aims to investigate patient characteristics influencing choice of antithrombotic treatment for stroke prevention in AF, and to collect data on clinical outcomes; three phases of the study will focus on anticoagulation use both before and after NOAC approval.<sup>36</sup> PREFER in AF (PREvention of thromboembolic events—European Registry in Atrial Fibrillation) is a multicentre, multinational, prospective observational disease registry involving more than 7000 patients with AF in seven European countries.<sup>37</sup> It aims to provide a detailed insight on the characteristics and management of patients with AF, along with patient satisfaction and quality-of-life data.<sup>37</sup> PREFER in VTE (PREvention of thromboembolic events—European

Registry in Venous Thromboembolism) is a prospective, observational, multicentre study that will investigate the management of VTE within the same seven European countries, with a final enrolment number of 3546 across 381 sites.<sup>38</sup> The EURObservational Research Programme Atrial Fibrillation (EORP-AF) Registry, undertaken by the European Society of Cardiology (ESC) is seeking to improve our understanding of AF epidemiology and management, and assess uptake process of the ESC guidelines to ultimately improve patient care.<sup>39</sup> EORP-AF is being performed in nine participating ESC member countries, with a target of 3000 consecutive in- and outpatients with AF presenting to cardiologists.<sup>39</sup> Data from the pilot registry have shown that NOAC use is increasing (7.7%), but remains low in the context of VKAs (72.2%).<sup>40</sup> A higher rate of NOAC use (specifically, rivaroxaban, and dabigatran) was associated with previous TIA/stroke ( $P = 0.0235$ ) and heart rhythm strategy ( $P = 0.0153$ ). Lower NOAC use was associated with valvular heart disease ( $P < 0.0001$ ), chronic heart failure ( $P = 0.0010$ ), coronary artery disease ( $P < 0.0001$ ), and peripheral artery disease ( $P = 0.0092$ ).<sup>40</sup> One-year follow-up data from the registry reinforces that optimal management of AF continues to pose a challenge, with a 1-year mortality rate of 5.7% in AF patients. Hospital readmissions were common, especially for AF and heart failure.<sup>41</sup>

Population-based studies and other national registries are also examining outcomes with NOACs as part of the ongoing commitment to elucidating their real-life safety. EXPAND is a Japanese, prospective, non-interventional, observational cohort study designed to investigate effectiveness and safety of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular AF in Japanese clinical practice (Clinicaltrials.gov identifier: NCT02147444). The study will enrol ~7000 patients diagnosed with non-valvular AF who are or will be treated with rivaroxaban for a follow-up period of 2 years.

The population-based Israeli Clalit Health Services database identified 18 249 patients who initiated anticoagulants for AF, showing that overall bleeding rates were largely similar between VKAs and NOACs, and importantly, intracranial haemorrhage (ICH) rates (per 100 patient-years) were lower with NOACs (rivaroxaban 20 mg OD (once daily): 0.27; dabigatran 150 mg BID (twice daily): 0.37; dabigatran 110 mg BID: 0.49) than with VKAs (0.70).<sup>42</sup> The largest increase in gastrointestinal bleeding rates (per 100 patient-years) was with dabigatran 110 mg BID (3.36) compared with rates of 1.88, 1.85, and 2.39 for VKAs, dabigatran 150 mg BID, and rivaroxaban, respectively.<sup>42</sup> A Danish modelling analysis calculated net clinical benefit (balancing the risk of ischaemic stroke against the risk of ICH) for three NOACs in stroke prevention in AF, using data from the Danish National Patient Registry.<sup>43</sup> In patients with a CHADS<sub>2</sub> score  $\geq 1$  or CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ , dabigatran, rivaroxaban, and apixaban were all superior to warfarin for net clinical benefit, regardless of risk of bleeding. When the risk of bleeding and stroke were both high, all three drugs had a greater net clinical benefit than warfarin.<sup>43</sup> In the USA, a large, retrospective pharmacovigilance study using

electronic medical records from the Department of Defence Military Health Service investigated the incidence of rivaroxaban-associated major bleeding in 27 476 patients with confirmed non-valvular AF.<sup>44</sup> A total of 496 major bleeding events occurred in 478 patients, which translated to an incidence of 2.86 per 100 person-years (95% CI 2.61–3.13).<sup>44</sup> The corresponding incidence of major bleeding rate in the Phase III ROCKET AF trial was 395 events in 7111 patients (3.6 per 100 person-years).<sup>20</sup> Patients who were classified as having major bleeding were older than the non-major bleeding group (mean age: 78.4 vs. 75.7 years). Patients with major bleeding had more comorbidities than those without, e.g. higher rates of hypertension, coronary artery disease, heart failure, and renal disease. In terms of their treatment, 63.2%, 32.3%, and 4.6% of patients in the major bleeding group were taking rivaroxaban 20 mg, 15 mg, and 10 mg, respectively. Gastrointestinal (88.5%) and intracranial (7.5%) bleeding constituted the most common types of bleeding. A total of 46.7% of patients with major bleeding received a transfusion, yet none had sufficient evidence of receiving any type of clotting factor. A total of 14 patients died during their hospitalization for major bleeding, yielding a fatal bleeding incidence rate of 0.08 per 100 person-years (95% CI 0.05–0.14). Data from this large database show that the real-world safety profile of rivaroxaban is consistently favourable, and supports outcomes observed in RCTs while presenting a low incidence of fatal bleeding.<sup>44</sup>

## Conclusion

Phase IV, non-interventional studies such as XAMOS, XANTUS, and XALIA as well as independent registries such as GARFIELD-AF, ORBIT-AF, and the Dresden NOAC registry help toward meeting the need for real-life data on the safety and effectiveness of rivaroxaban, and in particular confirming the safety of rivaroxaban in a routine practice setting. To date, more than 275 000 patients have been enrolled in clinical studies and registries with rivaroxaban. By the end of 2014, it was estimated that 12.5 million patients worldwide had received rivaroxaban since 2008 across the five licensed indications. This wealth of data should provide a substantial evidence base towards realising the favourable benefit–risk profile associated with rivaroxaban, and the advantages of such a regimen in ensuring patients receive a simple, effective treatment option that shows favourable safety outcomes.

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