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Rivaroxaban ▼ in non-valvular atrial fibrillation: European experience

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Rivaroxaban in non-valvular AF – UK experience in perspective

Diana A Gorog

ESC guidelines and differences between NOACs

Following the roll-out of the novel oral anticoagulants (NOACs), the European Society of Cardiology (ESC) published in 2012 a focused update of its guidelines for the management of atrial fibrillation (AF). Since the NOACs tested in clinical trials all showed at least non-inferiority when compared with vitamin K antagonists (VKAs), with a better safety profile, particularly with reduction in intracranial haemorrhage (ICH), the ESC 2012 guideline recommended NOACs as broadly preferable to VKAs in the vast majority of patients with non-valvular AF (NVAF).[1] In 2013, the European Heart Rhythm Association (EHRA) of the ESC published a practical guide on the use of NOACs, providing advice on various clinical scenarios, including initiation and follow-up, assessing anticoagulant effect, drug–drug interactions, switching between oral anticoagulants (OACs), management of bleeding, patients with chronic kidney disease, coronary disease, and those undergoing elective surgery, ablation or cardioversion.[2]

Due to the absence of head-to-head trials and heterogeneity in trial design, there was insufficient evidence to recommend one NOAC over another. However, there are practical differences between the agents available, which clinicians need to be familiar with.

1. Although all NOACs are licensed for stroke prevention in NVAF based on large, prospective randomised trials, there were important differences in trial design. The trial of dabigatran was not double blind,[3] unlike the studies with rivaroxaban[4] and apixaban,[5] and there were differences in baseline thromboembolic risk, which was highest in the ROCKET-AF study.[4] However, the primary end point of the studies was the same (total stroke and systemic embolism). Furthermore, dabigatran 150 mg b.i.d. and apixaban were shown to be superior to VKA,[3,5] whereas rivaroxaban and edoxaban have been shown to be non-inferior to VKA.[4,6] (Absolute risk reduction when compared with VKA ranged from 0.03–0.75.[3-5])
2. Renal excretion is higher with dabigatran, so particular caution is needed with dabigatran in patients with renal impairment.[3] None of the NOACs are indicated in severe or end-stage renal disease.
3. Cardioversion: it would appear reasonable to use NOACs for patients undergoing cardioversion, if compliance is considered reliable. A post-hoc analysis of patients undergoing cardioversion in the RE-LY, ROCKET-AF and ARISTOTLE studies showed that dabigatran (150 mg b.i.d.), rivaroxaban and apixaban were non-inferior to VKA.[7-9] A prospective study comparing rivaroxaban with VKA in patients undergoing cardioversion has been completed and is due to report in 2014,[10] and a study with apixaban is planned.
4. Absolute major bleeding events occurred less frequently with apixaban and low-dose dabigatran (110 mg b.i.d.) than with the other agents, with the caveat that this is based on non-head-to-head comparisons and definitions for bleeding outcomes were heterogeneous analyses.
5. Dosing: rivaroxaban is a once-a-day drug, whereas dabigatran and apixaban need to be taken twice daily. This may have an important impact on compliance.
6. Dosette box: dabigatran cannot be pre-packed into a Monitored Dosing System such as a dosette box, since dabigatran requires protection from moisture after being removed from the blister pack.[11] This may have important implications for the elderly, those with memory impairment or those whose carers administer and prepare their medications. Similarly, unlike rivaroxaban, dabigatran cannot be crushed, or put through a tube, immediately followed by enteric feeding, so may present issues for patients with swallowing difficulties.

Uptake in Europe versus US

Uptake of NOACs in the US was swift. After a year on the market, dabigatran, the first FDA-approved NOAC was being used in 16% of AF patients. By August 2012, more than 3.7 million US patients were taking dabigatran. Although in 2012, Japan and Australia issued safety warnings regarding the bleeding risk with dabigatran, the FDA released a report that year concluding that dabigatran does not present a higher bleeding risk than warfarin. However, more recent guidelines still back up the warnings of a higher bleeding risk.[12] Uptake in Europe has been slower. Two recently published registries show that NOAC use has increased in Europe after the publication of ESC guidelines, but use is still low. The EuroObservational Research Programme-Atrial Fibrillation (EORP-AF) Pilot General Registry results published in December 2013 showed that among 3,119 patients in nine European countries (not including the UK), some 80% overall received OACs, most often VKA (71.6%), with only 8.4% receiving a NOAC, although notably NOACs were not widely available in all countries.[13] The PREFER in AF registry (Prevention of thromboembolic events – European Registry in Atrial Fibrillation) of 7,243 patients in seven European countries, including the UK, showed that >80% of patients were anticoagulated, predominantly with VKA monotherapy (66.3%), and only 6.1% received a NOAC.[14]

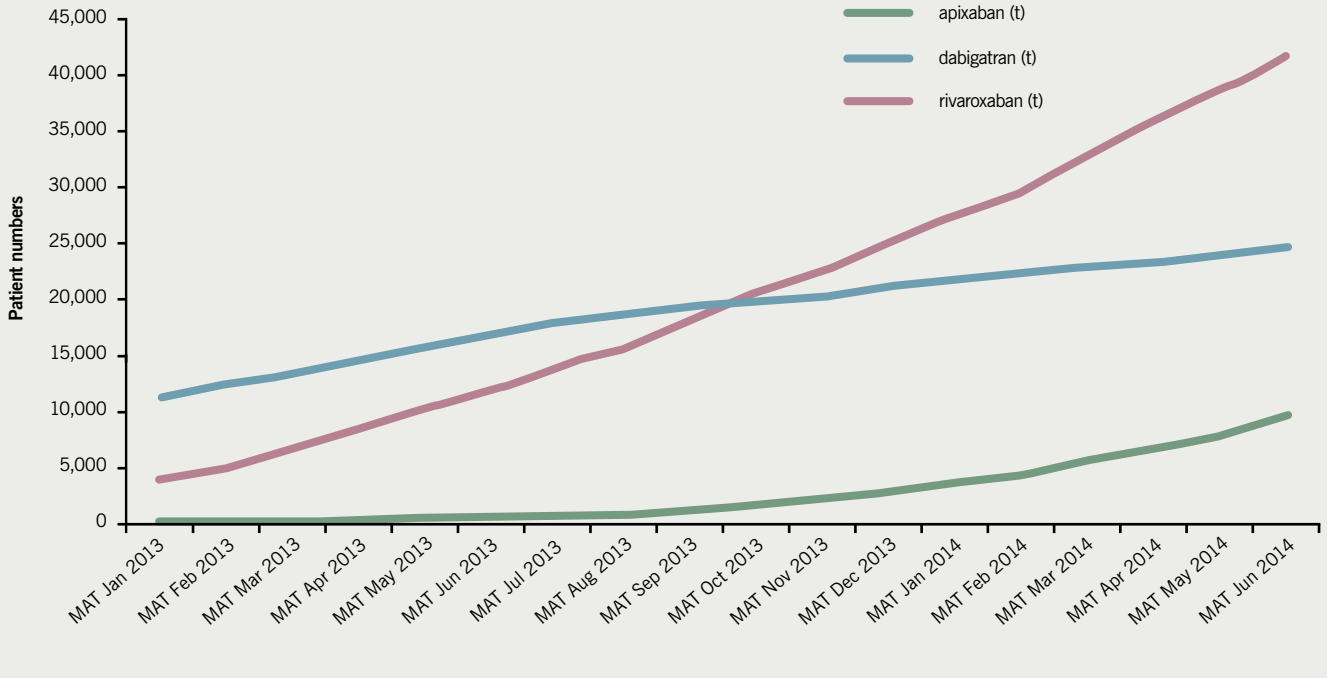
NOAC uptake in the UK

The National Institute for Health and Care Excellence (NICE) determines the cost-effectiveness of novel interventions. The incremental cost-effectiveness ratio (ICER) is the ratio of the change in costs to incremental benefits of a therapy, and used to guide decision-making in health economics. NICE's preferred form of ICER is the Quality Adjusted Life Year (QALY) gained by implementing the new intervention. NICE tends to accept as cost-effective those interventions with an ICER of <£20,000 per QALY.

NICE has published technology appraisals for all three NOACs, dabigatran in March 2012 (guidance.nice.org.uk/ta249), rivaroxaban in May 2012 (guidance.nice.org.uk/ta256) and apixaban in February 2013 (guidance.nice.org.uk/ta275), recommending each as an option for stroke prevention in patients with NVAF. All three agents are prescribed to patients with AF, with rivaroxaban being the most frequently prescribed NOAC in the UK from MAT October 2013 **(figure 1)**.[15] When NICE technology appraisal recommends use of a drug, the NHS must usually provide funding and resources for it within three months of the guidance publication, since the Department of Health considers the expected cost of implementing NICE Appraisal Guidance in setting the NHS budget. Yet, looking at the patient data, the proportion of AF patients prescribed NOACs in the UK is lower than in many European countries (4.1% – MAT December 2013).[15]

The introduction of a novel, expensive product can easily put pressure on a restricted prescribing budget. Thus, there is a need to agree priorities for NHS funding of therapies that compete for limited NHS resources. Local Medicine Management Committees

Figure 1. Novel oral anticoagulant (NOAC) patient numbers MAT – atrial fibrillation diagnosis 2013–14[15]



Key: MAT = moving annual total

(MMCs) have evolved and exist to facilitate consensus on the place of new drugs that have significant cost implications. MMCs make policy recommendations to primary and secondary care on the introduction of new drugs through evaluation of evidence and national guidance, to achieve cost-effective and equitable prescribing. The MMCs can also enforce generic substitution and restrictions on prescribing. Membership involves clinicians from secondary care, GP leads, pharmacists from primary and secondary care, non-clinical members of local commissioning groups and lay representatives.

Prescribing guidelines for NOACs by local MMCs vary significantly. Almost all recommend that VKAs remain the first choice of treatment for patients with AF, and NOACs are a second-line treatment. While it is agreed that NOACs should be considered as an alternative to warfarin in patients with AF, the wording of the level of stroke risk needed (e.g. $CHADS_2$ or CHA_2DS_2VASC scores) and the criteria for initiating a NOAC rather than VKA varies. Generally, adverse effects with VKAs, inability to comply with monitoring requirements, and time in therapeutic range (TTR <65%) seem agreed criteria for NOAC initiation/switch. However, there is disparity in whether to initiate a NOAC in someone who

has an ischaemic stroke on warfarin (with or without adequate TTR) and other groups such as those with excessive alcohol intake or those undergoing cardioversion. In fact, recent NICE guidance positions apixaban, dabigatran and rivaroxaban along with warfarin as first-line options.[16]

In an attempt to reduce spending on NOACs, many MMCs have chosen to highlight the negative aspects of these drugs (such as the lack of a clear antidote, or the difficulty in assessing compliance) and have played down the efficacy of NOACs in terms of stroke reduction, ICH and fatal bleeding profiles. Furthermore, although TTR may appear a logical inclusion, there is no significant evidence base for this being a significant criterion for treatment selection.

The variation among MMC guidelines and the lack of adherence to NICE and ESC 2012 recommendations, which recommend NOACs as broadly preferable to VKAs in the vast majority of patients with NVAF, and highlight the reduction in bleeding risk with NOACs, is a source of increasing frustration to many clinicians, especially in secondary care. A number of registries are under way that will provide real life longitudinal data on use, uptake and safety of OACs, including NOACs, such as GARFIELD, ROSE, and GLORIA-AF. We hope that reading/hearing about longer-term and broader use of NOACs will offer reassurance to UK practitioners – particularly around safety/bleeding profiles, and lead to increasing pressure on MMCs to adopt wider roll-out, to achieve the reduction in stroke and systemic embolism and intracranial bleeding, that all clinicians strive to achieve for their patients ●

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Rivaroxaban in non-valvular AF – French experience in perspective

Laurent Fauchier, Edouard Siméon, Christophe Saint-Etienne

Introduction

Vitamin K antagonists (VKAs) reduce the risk of stroke in patients with atrial fibrillation (AF). For more than five decades, they were the only available treatment. Novel oral anticoagulants (NOACs) have recently been approved for the prevention of non-valvular AF-related stroke. Dose-adjusted VKA therapy and NOACs are highly effective in AF patients. However, dabigatran, rivaroxaban and apixaban are more convenient, while at least equally effective and with a comparable safety profile (regarding bleeding complications) for stroke prevention compared with VKAs.[1-3]

Recent guidelines prefer treatment with NOACs over VKAs for most patients with non-valvular AF (NVAF) at thromboembolic risk, based on their net clinical benefit. Where an oral anticoagulant (OAC) is recommended for a patient with AF, but VKAs cannot be used, due to side effects or difficulties in keeping within therapeutic anticoagulation (INR 2–3), a NOAC should be chosen.[4] Whether a clear benefit also exists with NOACs in AF patients who previously did well with warfarin is still debated. Availability of NOACs and improved stroke and bleeding risk assessment should increase the number of AF patients who receive adequate thromboprophylaxis.

French perspective of the introduction of the NOACs

The European Committee for Medicinal Products for Human Use adopted a positive opinion for dabigatran and rivaroxaban in 2011. There was an additional consequent delay before marketing authorisation of these NOACs was granted in France. Reimbursement status was granted by the transparency commission of the National Authority for Health after a complete re-evaluation of therapeutic benefit. Several issues were discussed in depth: concern with regard to short experience, lack of monitoring and uncertainty with regard to dosing/adherence, the lack of antidote as yet, contraindications (e.g. valvular AF, low creatinine clearance), and expense to the healthcare system.


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Dabigatran and rivaroxaban, the first of the NOACs, were registered on the French refundable list with a 65% national reimbursement rate. Finally, the Economic Committee on Health Care Products established the price after discussion with the companies. The process neither led to a strong limitation of the drug labelling nor excluded certain patients from reimbursement. No spectacular new information appeared in the process, but several months were needed before clinicians were 'legally able' to prescribe dabigatran and rivaroxaban in France, in July and September 2012, respectively.

Changing prescribing habits and management of AF patients with rivaroxaban in France

Before prescribing a NOAC, a risk/benefit analysis has to be made on the basis of approved indications and on the preference of the patient after discussion of the options.

There are still clear practice differences for the use of NOACs for stroke prevention in AF among French physicians. While some aspects of the ESC guidelines on the use of NOACs for stroke prevention in AF are considered, VKA use decreases but still remains dominant, particularly for complex clinical scenarios. As part of a risk minimisation plan for rivaroxaban, there have been several interventions to deliver the key messages with, among others, a prescriber guide and a patient alert card. Dabigatran and rivaroxaban have a regular and similar increase in the overall volume of prescription anticoagulants.

How to differentiate between the licensed products?

All of the aforementioned NOACs are effective, have an acceptable tolerability profile and offer convenience.[1-3] The conclusion of indirect meta-

analyses about their relative efficacy and safety should be interpreted with caution but may impact clinicians. Ideally, clinical efficacy and safety should be compared head-to-head. Until then, physicians are relying on pharmacological properties and outcome data. The choice between NOACs is difficult and based on a variety of factors, some of which are evidence based, while many are not.

For patients with moderate renal impairment, one may consider the agents least dependent on renal function. In patients with acute coronary syndrome, rivaroxaban also has a positive effect there.[5] Dabigatran 150 mg b.i.d. markedly reduced ischaemic stroke and may be proposed after ischaemic stroke on VKA.[2] In case of dyspepsia, an agent with no reported gastrointestinal effects should be considered. Patient preference may lead to a once-daily formulation with rivaroxaban.

NOACs are non-inferior to or better than warfarin in terms of reducing stroke, intracranial haemorrhage and mortality.[1-3] They may be recommended for the majority of patients with NVAF, based on their net clinical benefit over VKAs. Discontinuation of therapy is apparently lower in patients who initiate NOAC treatment than in patients who begin warfarin treatment.[6] This possibly makes the treatment with the NOACs a cost-effective alternative to warfarin. Choice among NOACs may be influenced by drug characteristics and outcome trial results.

Finally, clinical development of the NOACs is not yet complete and important studies with rivaroxaban (e.g. X-VERT, X-TRA, PIONEER-AF, VENTURE-AF and XANTUS) will increase the breadth of experience in various cardiovascular conditions ●

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The French rivaroxaban experience: what we call progress is the exchange of one nuisance for another*

Thibault Leclerq, Samuel Goussot, Karim Stamboul, Yves Cottin, Luc Lorgis

*citation from Havelock Ellis 'Impressions and Comments'

Introduction

Rivaroxaban is an oral direct factor Xa inhibitor belonging to the novel oral anticoagulants (NOACs) class. Concerning efficacy and tolerability, it has been reported to be more effective than enoxaparin in preventing venous thromboembolism in patients undergoing orthopaedic surgery,[1,2] and was non-inferior to enoxaparin followed by warfarin in a study involving patients with established venous thrombosis.[3] Its good bioavailability, rapid-action and a half-life of 5–13 h,[4] associated with a highly reproducible anticoagulant activity and the same rate of bleeding complications as in patients on vitamin K antagonist (VKA) have led to its rapid uptake in clinical practice. The double-blind ROCKET-AF study established that rivaroxaban was non-inferior to warfarin for the primary end point of stroke and systemic embolism in 14,264 moderate-to-high-risk patients with non-valvular AF (NVAF) randomised to either (i) treatment with rivaroxaban 20 mg o.d. (15 mg daily for those with estimated creatinine clearance [CrCl] 30–49 ml/min) or (ii) warfarin.[5] Of note, the study population had a considerably higher risk of stroke than those in other NOAC AF trials. There was no reduction in rates of mortality or ischaemic stroke, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage for patients on rivaroxaban – although results showed an elevated risk of gastrointestinal bleeds.

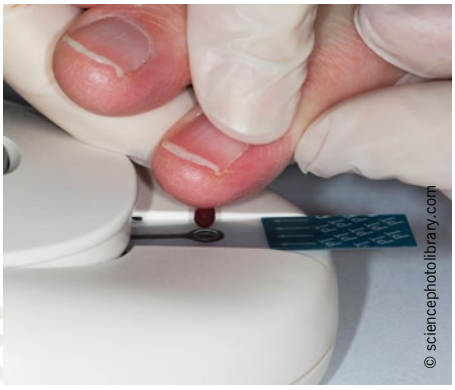
Despite an atmosphere of suspicion related to the succession of health scandals, French doctors have widely adopted this

new molecule as shown by a Conservatoire National des Arts et Métiers (CNAM) study showing a rise in the prescription of NOACs in the last quarter of 2012: among the 100,000 patients starting anticoagulant therapy, 57% were prescribed a first-line NOAC, and treatment was initiated by a cardiologist in 59% of cases. Therefore, NOACs have not replaced VKAs totally, but the key driver for the rapid uptake is that this innovation largely contributes to improving the care and quality of life for some patients. Unlike warfarin, rivaroxaban does not require laboratory monitoring, and to date, this is the only licensed molecule given once daily.

Despite some questions from patients (mostly related to anxiety brought about by information provided by the media and the internet), among the 368 patients who were switched from an anticoagulant agent to rivaroxaban, only five required a review of the treatment. Of these, three had developed digestive side effects, and two wished to return to their warfarin therapy despite good clinical tolerance. Major bleeding was rare, and in our clinical experience related to mistakes in the selection of patients. To reassure patients and their relatives, the pharmaceutical industry (XANTUS, XALIA studies) and health agencies have implemented unprecedented strategies to ensure proper use of the product and to identify possible side effects in a way that ensures real-world experience is as efficacious as clinical trial experience with these agents.

Furthermore, and to answer any questions that may arise with NOACs, the European Society of Cardiology (ESC) published a practical handbook on their use for stroke prevention in AF.[6] Of course, the obvious classical restrictions to such drugs remain: first, potential drug interactions justify precaution and it is strongly suggested that clinicians implement a therapeutic educational programme, as is the case for VKA. Second, such therapeutic programmes require the rigorous screening of patients: in patients with valvular AF, or severe liver or renal impairment (CrCl less than 15 ml Cockcroft/min), VKAs are as yet the only oral anticoagulant therapy indicated. As a precaution, this rule could be extended to patients with CrCl between 15 and 30 ml/min. However, depending on the methodology used to assess CrCl, results can be very different. This can make a huge difference and lead to prescription errors. It must be remembered that all of the clinical studies on anticoagulants showed that elderly people, especially women with low body weight, were particularly at risk of major bleeding events.

However, in the Einstein trial with rivaroxaban, rates of recurrent venous thromboembolism and bleeding were similar in the two study groups regardless of age, sex, presence or absence of obesity, level of renal function, or extent of pulmonary embolism. Although other options, such as MDRD or CKD-EPI, are now recommended for the assessment of glomerular filtration rate and are considered better estimators of renal function, the Cockcroft–Gault (CG) strategy offers two key benefits: this formula has been used in studies to select patients and to adjust dosages (15 mg/day below 50 ml/min and 20 mg/day above 50 ml/min in AF). However, with the Cockcroft formula, CrCl values in patients older than 75 years are systematically lower than values obtained with the MDRD formula.



To date, the biggest concern I hear from clinicians using the new agents is that no dedicated reversal agents are currently available. However, a direct factor Xa inhibitor, andexanet alfa (PRT 4445) is in development. The clinical situation remains a challenge, especially concerning the management of scheduled surgery. Whatever the type of surgery, and the level of risk of bleeding, caution should be the guiding principle. In the absence of clinical experience and simple laboratory tests, the surgery should be carefully managed, and protected if necessary by a bridging treatment with parenteral anticoagulants, although the necessity of this treatment is by no means absolute. Indeed, the pharmacokinetics of rivaroxaban in different individuals is not perfectly predictable and it cannot be certain that the drug has been completely eliminated within four days in every patient.[7]

Rivaroxaban is a promising drug. A twice-daily low dose (2.5 mg) reduced overall and cardiovascular mortality, thus bringing new hope to acute coronary syndrome (ACS) patients[8]

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Novel oral anticoagulants in daily clinical practice – German experience with rivaroxaban

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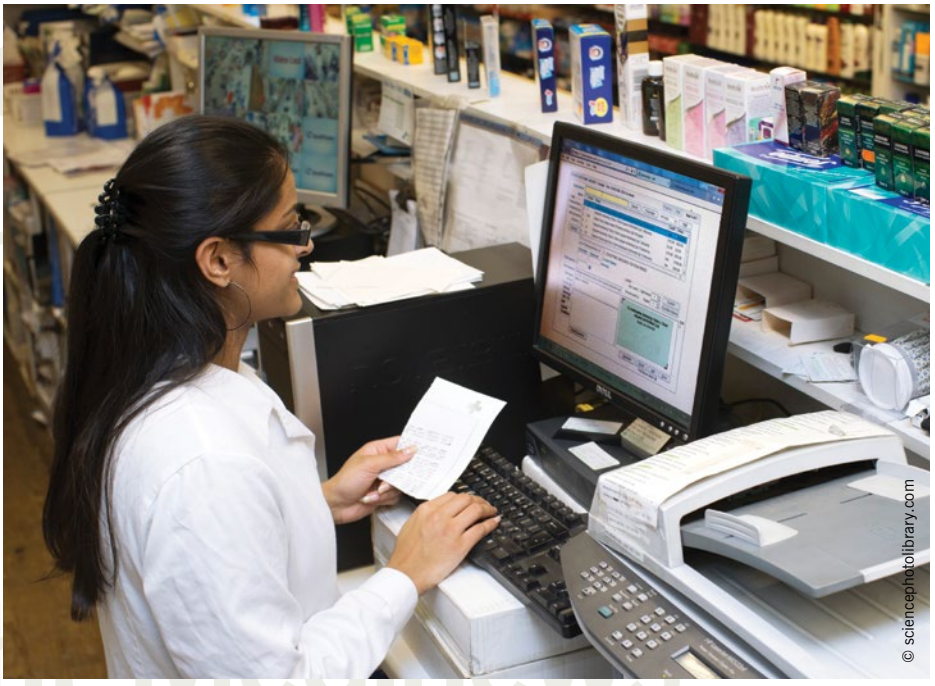
Summary

Oral anticoagulation has been restricted to vitamin K antagonists (VKAs) for more than 50 years. Starting in the last decade of the past century, central coagulation factors such as thrombin and factor Xa were explored as potential targets for the development of novel oral anticoagulants (NOACs). This led to the successful development and approval of a novel class of direct oral anticoagulants targeting factor Xa. Rivaroxaban was the first of the novel class of agents named 'xabans' that are direct oral factor Xa inhibitors. Since its initial approval for thromboembolic prophylaxis after hip and knee surgery in 2008, rivaroxaban also gained approval as an oral anticoagulant to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) in 2011 and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults in 2012. The single daily fixed dosing regimen for patients with NVAF offers a more convenient treatment option compared with VKAs.



Availability of NOACs in the clinic

Clinicians are well aware of the shortcomings of VKAs and every physician who routinely sees patients on long-term oral anticoagulation with VKAs has seen at least one severe bleeding, especially intracranial bleeding, as a major adverse event. Therefore, the development of NOACs[1] with a wider therapeutic window and no need for routine coagulation monitoring was eagerly awaited. The adverse events (liver failure) that have been observed with the oral direct thrombin inhibitor ximelagatran and the subsequent withdrawal of the drug did disappoint many clinicians. However, it did not break the enthusiasm; it even facilitated the intensive clinical development of alternative substances as NOACs. This ended successfully with the clinical approval of the first direct factor Xa inhibitor, rivaroxaban, as an oral anticoagulant.

Considerations regarding patient selection for NOACs

All of the NOACs are at least as effective in the prevention of stroke and systemic embolism as the VKAs.[2] However, in clinical studies there were significantly fewer intracranial and fatal bleeding events with NOACs compared with VKAs, although a statistically significant increase in the number of gastrointestinal bleeds, and a recent meta-analysis suggests a general net clinical benefit of NOACs over VKAs.[2] Despite this, there is currently no urgent need to switch every patient who fares well with a VKA to a NOAC. However, a switch should be considered in those patients with undulating INR values on VKA treatment or those with previous severe bleedings on VKA. In addition, there are some patients who do not want to accept the constraints of a VKA therapy and, therefore, actively ask for a NOAC therapy.

If a patient is to be initiated or switched to NOAC therapy, renal function needs to be taken into account. The direct thrombin inhibitor dabigatran etexilate is contraindicated if the creatinine clearance rate is below 30 ml/min. The direct Xa-inhibitor rivaroxaban may still be given at a reduced dose if creatinine clearance is below 30 ml/min, however, it is

contraindicated in patients with creatinine clearance rates below 15 ml/min.

Switching from VKA to rivaroxaban

The initiation of rivaroxaban for oral anticoagulation in VKA naive patients is simple. If the GFR is >49 ml/min, a once-daily oral dose of 20 mg rivaroxaban is sufficient for oral anticoagulation. In case of an acute PE, the patients should receive 15 mg rivaroxaban twice daily for three weeks followed by a 20 mg once-daily dose thereafter. Patients who are to be switched from VKA should stop taking the VKA and need to wait until the INR is equal or below 3.0 before starting oral anticoagulation with rivaroxaban 20 mg once daily.

Economic considerations

The successful development of novel medical therapeutics is a process that usually needs a time period of >10 years. The costs for the development period will have to be covered by the marketing of the new drug in the long term. In an ideal situation, the novel therapeutics will be more cost-effective in patient treatment compared with the standard therapy. The first cost-effectiveness analysis for the NOACs (including apixaban, dabigatran and rivaroxaban) indicated that all NOACs are more cost-effective compared with the VKA warfarin.[3] The cost for a one-year therapy with the NOACs and warfarin in the US served as the basis for this calculation. Given the current availability of more than one NOAC and the rules of the market, it appears to be likely that the costs for a therapy with NOACs will come down. Therefore, it may be expected that the NOACs, including rivaroxaban, are even more cost-effective compared with the standard therapy with VKAs in daily clinical practice.

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Outlook

In daily clinical practice we are currently in the luxurious situation that several NOACs have obtained clinical approval. One of the NOACs (dabigatran etexilate) belongs to the class of the direct thrombin inhibitors. The other two currently approved drugs (rivaroxaban and apixaban) belong to the group of the factor Xa inhibitors. Among them, rivaroxaban is the substance with the widest breadth of indications as a NOAC. In the near future we may see the clinical approval of another, edoxaban, as the phase III study ENGAGE-AF TIMI 48 has found edoxaban to be non-inferior to warfarin with respect to the prevention of stroke and systemic embolism.[4] Given the favourable outcomes in clinical trials with NOACs compared with INR guided therapy with VKAs, it is likely that data from daily clinical practice will confirm a general benefit of the NOACs compared with VKAs.

Therefore, the future challenges will include the choice of the best NOAC for the individual patient. As there are currently no direct clinical comparisons between the NOACs available, detailed clinical considerations (age, renal function, concomitant coronary artery disease, bleeding risk and risk for stroke or systemic embolism) will have to be taken into account. The range of the approved clinical indications, as well as the therapeutic window for the single agent, will also play a major role in guiding the physician's recommendation. Furthermore, the current development of a reversal agent (recombinant factor Xa lacking catalytic activity) that appears to be capable to reverse all (indirect or direct) factor Xa inhibitors[5] and the lack of a negative signal in patients with concomitant coronary artery disease for the oral direct Xa inhibitors in general[6] and a mortality reduction in the secondary prevention after acute coronary syndrome (ACS) with rivaroxaban[7] may point the future direction in the use of NOACs in daily clinical practice ●

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European experiences reviewed

David Hargroves

Background

The novel oral anticoagulant (NOAC) agents (dabigatran, rivaroxaban, apixaban) have had a disproportionally poor uptake since their respective launches and National Institute for Health and Care Excellence (NICE) Technology Appraisal in the UK between 2012 and 2013 for their use in stroke prevention in patients with non-valvular atrial fibrillation (NVAF), when compared with our European counterparts; particularly Germany, Holland and France. In the original NICE economic analyses for the NOACs there was a calculated uptake of approximately 20% in the first year,[1] the figure currently runs at <8% with many area's significantly lower.[2]

Why the delay in uptake in the UK?

The use of anticoagulation in atrial fibrillation (AF) in the UK has been disproportionately poor for many years. Failure to recognise the benefits of anticoagulation has been reinforced historically through the failure to financially reward vitamin K anatgonist (VKA) prescribing through the Quality and Outcomes Framework (QOF). There is a paradigm shift required in the understanding within UK general practice/general internal medicine to appreciate that anticoagulation should be a default treatment for all but the very-low-risk patients (CHADSVASc <1) with AF. Once this message is clearly accepted then movement towards anticoagulation agents, specifically those with good safety profiles (NOACs) may be easier.

There are many challenges involved in the uptake of new agents, particularly so in the UK. As a medical society we are proud of our cautious response to potentially hazardous innovations.

The funding of healthcare in the UK is unique. The National Health Service (NHS) reforms in 2012 placed the responsibility for continued prescribing firmly with commissioning clinical commissioning groups (CCGs). This may negatively incentivise high-cost healthcare reform. The lack of a joint social and health budget places all the cost of healthcare interventions upon a commissioning CCG; whom in themselves would not see a benefit from the overall saving to both social and healthcare of an innovation.

Summary

The significant experience that European prescribers report from the use of the NOACs, and in particular rivaroxaban, is most encouraging. These reports should reassure UK prescribers of the safety profile and low bleeding incidence in real-world populations.

Many of the concerns listed by European colleagues regarding the prescription of NOACs are universal and extend to the UK. A real fear of the complications from prescriptions without the reassurance of compliance monitoring that occurs with VKA is often cited, as is the lack of an antidote currently ●

Key differences of NOACs

There are no head-to-head studies between the NOACs and, therefore, comparisons between the agents are very difficult. The published meta-analyses are helpful.[4] In real-world prescribing, however, rivaroxaban has a once-daily formulation, safety data in renal impairment and published experience in its use with co-existent coronary disease in acute coronary syndromes.[5,6] Familiarity of prescribing rivaroxaban within its other licenced indications may help build confidence in its use in AF.

Secondary care role

There is a key role for secondary care in the UK to improve the management of stroke prevention in patients with AF. There is a real need for continued education to raise awareness of the published evidence of anticoagulation efficacy versus antiplatelet therapy, and the comparable efficacy and safety profiles of the NOAC agents compared to VKAs. The cost-effectiveness modelling needs to be communicated to commissioning medicines management agencies focusing upon previously excluded benefits: e.g. reduction in hospitalisation costs and ongoing care costs for those patients no longer at risk of major haemorrhage.

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▼ **This medicinal product is subject to additional monitoring**

Xarelto® 2.5, 10, 15 and 20 mg film-coated tablets (rivaroxaban)
Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet. **Indication(s):** *2.5mg* - Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. *10mg* - Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. *15mg/20mg* - 1. Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *2.5mg* - Dosage 2.5 mg rivaroxaban orally twice daily; patients should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Start Xarelto as soon as possible after stabilisation, including revascularisation for ACS; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation. If dose is missed take next dose, do not double the dose. *10mg* - Dosage 10 mg rivaroxaban orally once daily; initial dose should be taken 6 to 10 hours after surgery provided haemostasis established. *Recommended treatment duration:* Dependent on individual risk of patient for VTE determined by type of orthopaedic surgery: for major hip surgery 5 weeks; for major knee surgery 2 weeks. *15mg/20mg - SPAF:* 20 mg orally *o.d.* with food. *DVT & PE:* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; take with food. *All strengths* - Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. For patients who are unable to swallow whole tablets, refer to SmPC for alternative methods of oral administration. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment; *2.5mg /10mg* - moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. Severe (creatinine clearance 15-29ml/min) - limited data indicate rivaroxaban concentrations are significantly increased, use with caution. *15mg/20mg* - moderate & severe renal impairment - limited data indicate rivaroxaban plasma concentrations are significantly increased, use with caution – *SPAF*: reduce dose to 15mg *o.d.*, *DVT & PE:* 15 mg *b.i.d.* for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg *o.d.* if patient's bleeding risk outweighs risk for recurrent DVT & PE; *All strengths* - Creatinine clearance <15 ml/min - not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except when switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. *2.5mg* - concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; **Warnings & precautions:** *2.5mg* Treatment in combination with antiplatelet agents other than ASA & clopidogrel/ticlopidine has not been studied & is not recommended. Clinical surveillance in line with anticoagulation practice is recommended throughout treatment. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy – haemoglobin/haematocrit testing may be of value to detect occult bleeding. Use is not recommended in patients: with creatinine clearance <15 ml/min; receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with increased bleeding risk (refer to SmPC); concomitantly treated with dronedarone. Use with caution in patients: with conditions with increased risk of haemorrhage (refer to SmPC); with severe renal impairment; with moderate renal impairment concomitantly receiving other medicines which increase rivaroxaban plasma concentrations; treated concomitantly with medicines affecting haemostasis; in ACS patients > 75 years of age or with low body weight (<60kg). Patients on treatment with Xarelto & ASA or Xarelto & ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations. *10mg* - Not recommended in patients: undergoing hip fracture surgery; receiving concomitant systemic treatment with strong CYP3A4 and P-gp inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with creatinine clearance <15 ml/min. Please note - Increased risk of bleeding therefore careful monitoring for signs/symptoms of bleeding complications & anaemia required after treatment initiation in patients: with severe renal impairment; with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; treated concomitantly with medicinal products affecting haemostasis; with congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease (consider appropriate prophylactic treatment for at risk patients), vascular retinopathy, bronchiectasis or history of pulmonary bleeding. Take special care when neuraxial anaesthesia or spinal/epidural puncture is employed due to risk of epidural or spinal haematoma with potential neurologic complications. *15mg/20mg* - Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. The following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation so use with caution: in patients with severe renal impairment or with renal impairment concomitantly receiving medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicines affecting haemostasis. Use is not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. *10mg/15mg/20mg* - There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. *All strengths - Elderly population* – Increasing age may increase haemorrhagic risk. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving NSAIDs, ASA or platelet aggregation inhibitors due to the increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs and symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, angioedema and allergic oedema, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** *2.5mg* - 56 tablets: £58.80 & 100 tablets: £105.00. *10mg* - 10 tablets: £21.00, 30 tablets: £63.00 and 100 tablets: £210.00. *15mg* – 14 tablets: £29.40, 28 tablets: £58.80, 42 tablets: £88.20, 100 tablets: £210.00; *20mg* – 28 tablets: £58.80, 100 tablets £210.00 **MA Number(s):** *2.5mg* - EU/1/08/472/025-035. *10mg* - EU/1/08/472/001-10, *15mg/20mg* - EU/1/08/472/011-21 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** January 2014.

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