Extension Treatment: Preventing Recurrence of Venous Thromboembolism

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Interview Summary

A conversation with David Sutton, co-director of the Staffordshire Thrombosis and Anticoagulation Centre, University Hospitals North Midlands, UK, and Sue Rhodes, venous thromboembolism (VTE) clinical nurse specialist and joint Anticoagulant Lead at Great Western Hospitals, Swindon, UK.

VTE is one of the major causes of morbidity and mortality, and is still a bigger killer than breast cancer, prostate cancer, and road traffic accidents.[1] While there has been little change in the number of cases since 2010, treatment options have improved. EMJ talked to thromboembolism experts about VTE extension treatment and its role in preventing recurrence.

HOW DOES VENOUS THROMBOEMBOLISM AFFECT PATIENTS?

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 1–2 in every 1,000 people annually.[2] It is a major cause of death and disability in England, with thousands of deaths directly attributed to the condition each year.[3] Following a VTE, patients and clinicians face complex decisions about how to manage risk of recurrence over their lifetimes. Sutton and Rhodes explained how decisions relating to risk of recurrence are discussed with patients who have presented with a first episode of VTE.

Sutton challenged a common misconception about VTE: "It's not just an acute event. VTE often has lifelong implications for patients." These implications may include associated health

issues such as post-thrombotic syndrome, risk of recurrence, and psychological distress.

The psychological impact of a VTE event can be significant, and is linked both to the event itself, its management, and fear of recurrence. Evidence shows a post-traumatic stress-like response in some patients, especially those who experienced PE.[4]

Sutton explained how the 'information void' contributes to anxiety in VTE patients: "Patients often don't get the information or follow-up that they need. They're often treated in and out of hospital in the same day," which is helpful from a treatment perspective, but doesn't allow for a longer discussion with the patient about their individual risk of recurrence. They also cautioned against the use of exaggerated or fatalistic language, which elevates patients' concerns. "We get very anxious-looking doctors saying: 'Oh, it's a big clot, we're very worried, we need to scan you straight away.' By default, how we communicate VTE diagnosis to patients could help reduce psychological distress."

MANAGING RISK OF RECURRENCE IN VENOUS THROMBOEMBOLISM

Management of VTE depends on the individual and their unique risk profile. Causation is a good place to start when assessing risk of recurrence. There are many causes of VTE, some of which are classified as 'provoked', such as major surgery, trauma, or cancer; and others as 'unprovoked', with no apparent risk factors. Hospitalisation in general is a known risk factor, while other factors such as age, bodyweight and mobility, and comorbidities may combine to form cumulative risk.[5] Whether VTE is provoked or unprovoked has an impact on risk of recurrence.[6]

"Patients with an unprovoked VTE have a one in 10 risk of recurrence within 1 year of stopping anticoagulants and as high as 50% over 5–10 years, varying based on sex, bodyweight, and other individual factors," said Sutton.

The risk of recurrence in patients with a provoked VTE is much lower. "For patients with major transient provocations such as surgery or a major trauma, recurrence rate after stopping anticoagulants is generally less than 1%," they said.

However, the situation is not black and white. Risk of recurrence is on a scale, depending on the type of VTE event and a person's individual risk factors. Provocations can be major or minor, transient, or persistent (Figure 1).[6]

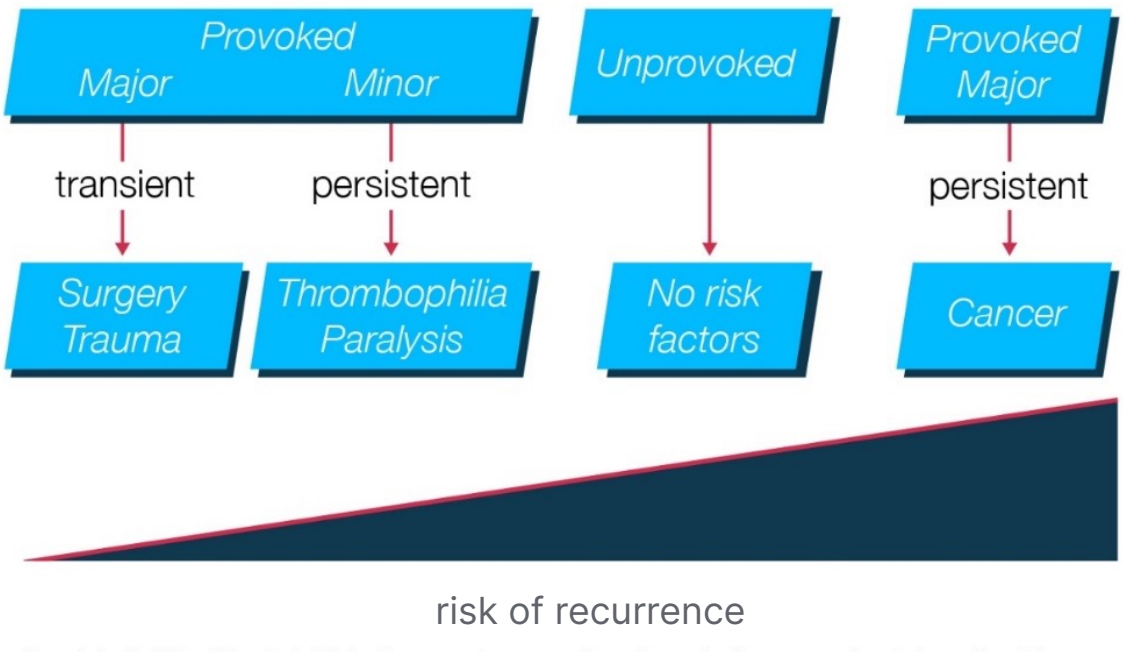
Rhodes added that there is no exact formula for determining risk, which is why individual patient reviews with a thromboembolism specialist are crucial, either in a thrombosis clinic or a specialist anticoagulant clinic. "We start by asking the patient what their symptoms were, whether there was any reason for developing a clot (provoking factors), and if they or an immediate member of their family has had a clot before. Then we try and establish whether the clot was definitely unprovoked, and then work through the patient's individual risk of recurrence before deciding on the length of duration of anticoagulant treatment."

TREATING VENOUS THROMBOEMBOLISM: THE ROLE OF EXTENDED THERAPY

Anticoagulation therapy is the first-line treatment of choice for both the treatment and prevention of VTE, including DVT and/or PE.[6] Most patients with VTE provoked by transient risk factors such as surgery or trauma are recommended to receive 3 months of anticoagulant therapy, as their risk of recurrence is low.[2] VTE provoked by a major persistent risk factor such as cancer, or those considered to have 'unprovoked' VTE, have a higher risk of recurrence if anticoagulants are stopped. In these patients, extended treatment may be needed.[2,7]

So, what is extended treatment? "My definition of extended is really anything beyond that initial 3 months of mandated treatment," answered Sutton. Its primary aim is prevention of recurrence in higher risk patients. "The aim is stopping a new clot from developing and that risk can be indefinite, so it needs to be reviewed annually or more frequently,"[8] they added. "I avoid the use of the phrase 'lifelong anticoagulation', because this implies no further reviews are needed."

Figure 1: Risk of recurrence.



Adapted from Prins et al.[6]

Data show the benefit of extended treatment with reduced doses of direct oral anticoagulants (DOAC). In the EINSTEIN-Extension study, rivaroxaban 20 mg was compared to placebo for an additional 6–12 months, in patients who had completed 6–12 months of treatment for VTE and were in clinical equipoise regarding the need for continued anticoagulation. Rivaroxaban had a non-inferior efficacy with respect to the primary outcome (36 events [2.1%], versus 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; p<0.001)[2,9] (Table 1). Four patients in the rivaroxaban group had non-fatal major bleeding (0.7%), versus none in the placebo group (p=0.11).[2,9] Meanwhile, in EINSTEIN-Choice, patients who had completed 6–12 months of treatment for VTE and were in clinical equipoise regarding the need for continued anticoagulation, received either rivaroxaban 20 mg or 10 mg, or aspirin 100 mg. Both doses of rivaroxaban showed a significant reduction in VTE recurrence versus aspirin with comparable rates of major bleeding, extending the benefit–risk profile of the treatment beyond the full-dose regimen[7] (Table 2).

"EINSTEIN-Choice was useful because it included people with provoked thrombosis who wanted to continue anticoagulant therapy," Sutton said. "It gives some reassurance that these people with a lesser provocation may also benefit from longer-term anticoagulation."

The ability to tailor the dose of anticoagulation based on patients' individual risk factors is another benefit of extended DOAC therapy. "One hat doesn't fit all," said Rhodes, adding that in certain patients, a higher dose of DOAC may be more appropriate. For example, stated Sutton, "patients with obesity or severe post-thrombotic syndrome, and haematology patients with myeloproliferative disorders."

Anticoagulation therapy has come a long way. Rhodes described how having more therapies has improved quality of life for VTE patients. "Having DOACs has been revolutionary, especially for patients who had a DVT or PE in the past, when the only option was low molecular weight heparin and warfarin. The range of DOACs that are available ensures that we are choosing the right intervention for the right patient."

Table 1 : EINSTEIN-Extension study summary results table. Oral rivarobaxan for symptomatic venous thromboembolism.

Clinical outcomes in the continued treatment study.*				
Outcome	**Rivaroxaban no. (%)**	**Placebo no. (%)**	**Hazard ratio (95% CI)**	**p**
Efficacy				
Intention-to-treat population	602	594	N/A	N/A
Recurrent VTE**	8 (1.3)	42 (7.1)†	0.18 (0.09–0.39)	<0.001
Type of recurrent VTE				
Fatal PE	0	1	N/A	N/A
PE could not be ruled out	1	0	N/A	N/A
Non-fatal PE	2	13	N/A	N/A
Recurrent DVT	5	31	N/A	N/A
Safety				
Safety population	598	590	N/A	N/A
First major or clinically relevant non-major bleeding	36 (6.0)	7 (1.2)	5.19 (2.3–11.7)	<0.001
Major bleeding†	4 (0.7)‡	0	N/A	0.110
Contributing to death	0	0	N/A	N/A
In a critical site	0	0	N/A	N/A
Associated with a fall in haemoglobin of ≥2 g per dL, transfusion of ≥2 units, or both	4	0	N/A	N/A
Clinically relevant non-major bleeding†	32 (5.4)‡	7 (1.2)	N/A	N/A
Haematuria	9	0	N/A	N/A
Epistaxis	8	1	N/A	N/A
Rectal	7	2	N/A	N/A
Skin	4	2	N/A	N/A
Uterine	3	2	N/A	N/A
Gastrointestinal	1	0	N/A	N/A
Related to tooth extraction	1	0	N/A	N/A
Ear	1	0	N/A	N/A
Total deaths	1 (0.2)	2 (0.3)	N/A	N/A
PE, or PE not ruled out	1	1	N/A	N/A
Bleeding	0	0	N/A	N/A
Cancer	0	1	N/A	N/A

Table 1 continued: EINSTEIN-Extension study summary results table. Oral rivarobaxan for symptomatic venous thromboembolism.

Clinical outcomes in the continued treatment study.*				
Outcome	**Rivaroxaban no. (%)**	**Placebo no. (%)**	**Hazard ratio (95% CI)**	**p**
Cardiovascular disease	0	0	N/A	N/A
Other	0	0	N/A	N/A

* Hazard ratios are for rivarobaxan as compared with placebo.

** Symptomatic, recurrent VTE, defined as the composite of DVT, or non-fatal or fatal PE.

† Some patients had more than one event.

‡ All four patients with major bleeding (gastrointestinal in three and menorrhagic in one) and six of the 32 patients with clinically relevant non-major bleeding discontinued treatment permanently.

Adapted from Bauersachs et al.[9]

CI: confidence interval; DVT: deep vein thrombosis; N/A: not applicable; PE: pulmonary embolism; VTE: venous thromboembolism.

Deciding when to prescribe extended therapy may appear straightforward, but there is a vast grey area. Referring to the risk of recurrence scale, Rhodes said: "On the left you have patients who are low risk, and we would stop their treatment at 3 months. On the right are patients with persistent risk factors, who could benefit from long-term treatment. Many patients fall into the middle 'grey' zone and the best course of treatment depends on which individual risk factors they have."

WEIGHING UP RISK OF RECURRENCE AND RISK OF BLEEDING

While for many patients the benefits of anticoagulation therapy often outweigh the risks,[11] for others, the potential adverse effects of extended DOAC treatment incite fear and a reluctance to continue therapy beyond 3 months. "Risk of bleeding is the main worry," said Rhodes, referring to the increased risk of haemorrhage due to hindrance of clotting ability with DOAC use.[7]

"We have to weigh up that risk of bleeding with the risk posed by recurrence for that individual, but also consider how they feel about those risks,"[2,7,10,12] they said, stressing the importance of open dialogue with the patient.

Rhodes said expertise is key. "The conversation with the patient needs to be from someone who manages anticoagulation and venous thromboembolism on a regular basis. You need someone with the confidence to know what they are talking about in terms of explaining individual risk to a patient. It is important that we try to get it right the first time with our explanation, so that the patient feels confident in the decisions made."

Their approach is multi-dimensional. "We include the patient in the decision-making process, as they can be a strong influencer of the treatment. Generally, if a parent or close relative has had a clot before, then the patient is usually keen to stay on anticoagulation and we would not normally decline continuing treatment as long as the patient is aware of the risks. On the flip side of that, if they have experienced a bleed then they are keen to stop anticoagulation. We allow time for the patient to absorb the information relating to their individual risk to help them make the most appropriate decision. We always leave the door open for them to come back and go through things again, and sometimes they may change their minds, but we are always there to support."

"The way I phrase it to patients is that the risk of bleeding with extended duration anticoagulation is comparable to aspirin in the long-term," said

Table 2: Rates of recurrent venous thromboembolism and major bleeding, according to risk profile and duration of anticoagulation before randomisation.

Variable	Rivaroxaban 20 mg (N=1,107)		Rivaroxaban 10 mg (N=1,127)		Aspirin 100 mg (n=1,131)	
	Recurrent VTE	Major bleeding	Recurrent VTE	Major bleeding	Recurrent VTE	Major bleeding
	number/total number (%)					
Risk profile						
Provoked index event	9/666 (1.4)	2/666 (0.3)	6/647 (0.9)	3/647 (0.5)	24/663 (3.6)	2/663 (0.3)
Unprovoked index event	8/441 (1.8)	4/411 (0.9)	7/480 (1.5)	2/480 (0.4)	26/468 (5.6)	1/468 (0.2)
Previous VTE						
Yes	3/198 (1.5)	2/198 (1.0)	2/197 (1.0)	0/197	17/194 (8.8)	1/194 (0.5)
No	14/909 (1.5)	4/909 (0.4)	11/930 (1.2)	5/930 (0.5)	33/937 (3.5)	2/937 (0.2)
Duration of anticoagulation before randomisation						
<9 mo	12/774 (1.6)	3/774 (0.4)	7/782 (0.9)	3/782 (0.4)	35/793 (4.4)	3/793 (0.4)
≥9 mo	5/333 (1/5)	3/333 (0.9)	6/345 (1.7)	2/345 (0.6)	15/338 (4.4)	0/338

* Recurrent VTE was assessed in the intention-to-treat population. Major bleeding was assessed in the same population but during the period of study-drug administration plus a window of 2 days.

Adapted from Weiz et al.[10]

VTE: venous thromboembolism.

Sutton. They also stressed the importance of allowing patients time to think and digest information. "Try not to make the patients feel they are making a lifelong decision in the consultation," they advised.

Sutton added that some elements of bleeding risk may be modifiable if effective follow-up is actioned. "Having an anticoagulant clinical nurse specialist team follow-up, you can pick up the inappropriate aspirin, the selective serotonin reuptake inhibitor without a protein pump inhibitor, all the things you can do to modify risk of bleeding." Rhodes agreed, stating they review patients on an annual basis, sometimes more frequently if renal function is impaired, to ensure it is appropriate to continue with anticoagulation.

"Getting It Right First Time," as Rhodes said, may help to instill good habits in patients, and "counselling patients is really important to good long-term compliance," said Sutton. "If they know why they are taking a drug, know the risks and the risk of recurrence, it improves that longer-

term use." However, VTE management outside of the specialist team can be a concern, which may lead to out-of-date treatment protocols or incorrect management. Patients moving between teams, especially during hospital admission and discharge, can be a challenge, and sometimes anticoagulation can be stopped inappropriately with no follow-up in place to ensure it is restarted. "The problem is, there's no good blood test to say it's appropriate to stop anticoagulant therapy, only to indicate risk," said Sutton. Lastly, VTE risk is not static, it changes over time, meaning long-term follow-up with a specialist is vital. "There's always a reason to keep reviewing," said Sutton.

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Xarelto® (rivaroxaban) 2.5, 10, 15 and 20mg film-coated tablets & 1mg/ml granules for oral suspension
Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet & 1mg/ml granules for oral suspension. **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. Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. *10mg* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *15mg/20mg* 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). Treatment of DVT & PE, & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *Paediatrics: 1mg/ml* – Treatment of VTE and prevention of VTE recurrence in term neonates, infants & toddlers, children, & adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment. Treatment of VTE & prevention of VTE recurrence in children & adolescents aged less than 18 years & weighing from 30 kg to 50 kg (for 15 mg) / above 50 kg (for 20 mg) after at least 5 days of initial parenteral anticoagulation treatment. **Posology & method of administration:** *2.5mg* – Oral *b.i.d.* dose; 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, and should not be started until haemostasis is achieved in successful lower limb revascularisation for symptomatic PAD; 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 – hip or knee replacement surgery:* Oral *o.d.* dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. *DVT & PE:* When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg *o.d.*. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg *o.d.*, a dose of Xarelto 20 mg *o.d.* should be considered. *15mg/20mg* – Take with food *SPAF:* 20 mg orally *o.d. DVT & PE:* Adults – 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; Children & adolescents – calculate dose based on body weight: body weight <30kg refer to the SmPC for Xarelto 1mg/ml granules for oral suspension; body weight 30-50kg take 15mg *o.d.*; body weight >50kg take 20mg *o.d.*. Monitor child's weight & review regularly. Xarelto is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence. *All strengths* – Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Special populations:*** Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement: There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation & undergo PCI with stent placement. ***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. *15mg/20mg* – adults with moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29ml/min) – *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; children & adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2) – not recommended; *All strengths* – Severe impairment: limited data indicate rivaroxaban concentrations are significantly increased, use with caution. 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 ***Paediatrics:*** Only for treatment of VTE & prevention of VTE recurrence. **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 under specific circumstances of switching anticoagulant therapy 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. Presence of malignant neoplasms at high risk of bleeding. *2.5mg* – concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. **Warnings & precautions (W&P):** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. Patients with active cancer: the individual benefit of antithrombotic treatment should be weighed against the risk for bleeding. Gastrointestinal or genitourinary tract tumours have been associated with an increased risk of bleeding. Patients with CAD/PAD: after recent revascularisation procedure of the lower limb due to symptomatic PAD, if required, a dual antiplatelet therapy with clopidogrel, should be short-term, long-term dual antiplatelet therapy should be avoided. Xarelto in combination with other antiplatelets is not recommended. Xarelto should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions. 1mg/ml oral suspension – sodium benzoate may increase jaundice in newborn infants (up to 4 weeks old). *Not recommended:* in patients with an increased bleeding risk (refer to SmPC); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- & P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with prosthetic heart valves; for patients with a history of thrombosis diagnosed with antiphospholipid syndrome; Xarelto should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR); *2.5mg* treatment in combination with antiplatelet agents other than ASA & clopidogrel/ticlopidine, patients after recent lower limb revascularisation procedures due to symptomatic PAD with a previous stroke or TIA receiving dual antiplatelet therapy; *10mg/15mg/20mg* in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy; *1mg/1ml* in children less than 6 months of age who at birth had <37 weeks of gestation, a body weight of <2.6 kg, or had <10 days of oral feeding; in children ≥1 year old with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2); in children ≤1 year old with serum creatinine results >97.5th percentile. *Use with caution:* in patients treated concomitantly with medicines affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed; in patients at risk of ulcerative gastrointestinal disease (prophylactic treatment may be considered); *2.5mg* in patients ≥75 years of age or with lower body weight (<60kg); in CAD patients with severe symptomatic heart failure. 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. *2.5mg/10mg* in patients with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *15mg/20mg* in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *1mg/ml* in children with cerebral vein & sinus thrombosis who have a CNS infection. *All strengths* – 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. Xarelto tablets 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; use with caution in patients concomitantly receiving SSRIs/SNRIs due to a possible increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive & use machines:** syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache (in children: very common), eye haemorrhage, hypotension, haematoma, epistaxis (in children: very common), haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting (in children: very common), increase in transaminases, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common* in women <55 yrs treated for DVT, PE & prevention of recurrence, common in female adolescents after menarche), renal impairment, fever (in children: very common), peripheral oedema, decreased general strength & energy, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings & Precautions – in addition:* thrombocytosis, thrombocytopenia (in children: common), Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome, anaphylactic reactions including shock, angioedema & 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 (in children: common), hepatic impairment, cholestasis & hepatitis (incl. hepatocellular injury), increases in bilirubin (in children: common), blood alkaline phosphatase & GGT, increased conjugated bilirubin, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention, eosinophilic pneumonia. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** In the case of an overdose, the patient should be observed carefully for bleeding complications and other adverse reactions. A specific reversal agent is available, refer to the SmPC for andexanet alfa. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *2.5mg* – 56 tablets: £50.40. *10mg* - 10 tablets: £18.00, 30 tablets: £54.00 & 100 tablets: £180.00. *15mg* – 14 tablets: £25.20, 28 tablets: £50.40, 42 tablets: £75.60, 100 tablets: £180.00; *20mg* – 28 tablets: £50.40, 100 tablets £180.00; Treatment Initiation pack (42 tablets of 15mg, 7 tablets of 20mg): £88.20 *1mg/ml* – 100ml bottle (50ml reconstituted): £9.00, 250ml bottle (100ml reconstituted): £18.00 **MA Number(s):** *Great Britain: 2.5mg* – PLGB 00010/0708. *10mg* – PLGB 00010/0705. *15/20mg* – PLGB 00010/0706, 0707, 0709. *1mg/ml* – PLGB 00010/0746. *Northern Ireland: 2.5mg* – EU/1/08/472/025-035, 041, 046-047. *10mg* – EU/1/08/472/001-010, 022, 042-045 *15mg/20mg* – EU/1/08/472/011-016, 017-021, 023-024, 036-040, 048-049. *1mg/ml* – EU/1/08/472/050-051 **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD, U.K. Telephone: 0118 206 3000. **Date of preparation:** January 2023

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Adverse events should be reported.
Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store.
Adverse events should also be reported to Bayer plc.
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