Rivaroxaban

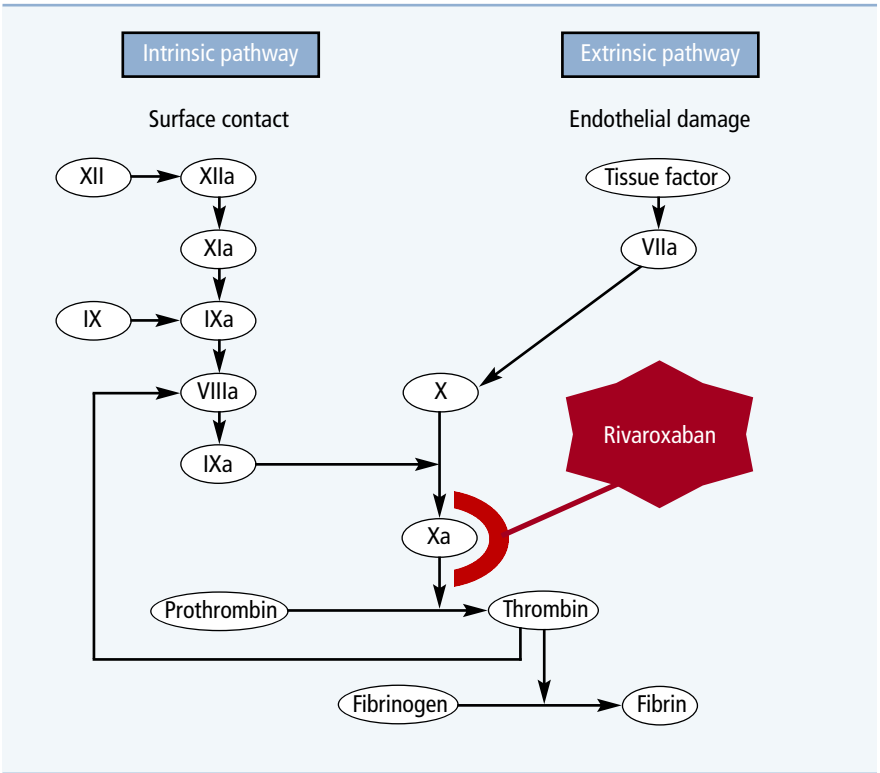

Figure 1. The pharmacological action of rivaroxaban

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Introduction

Cardiovascular and stroke disease are the leading cause of morbidity and mortality in diabetes, with management centred on reducing risk. Atrial fibrillation (AF), the most common cardiac arrhythmia worldwide, has a higher prevalence in diabetes and is associated with a five-fold increase in risk of stroke. The pathophysiology behind adverse outcomes in patients with AF is largely secondary to thromboembolic phenomena and hence appropriate anticoagulation is essential to management.

Warfarin has been the drug of choice for this over the past 50 years but dosing can be problematic due to unpredictable pharmacokinetics and potential drug interactions. Recent research has focused upon designing anticoagulants with more predictable therapeutic properties, such as the direct-Xa inhibitors and thrombin inhibitors. Rivaroxaban is the first oral direct-Xa inhibitor made available in the UK. While initial licensing centred on venous thromboembolism (VTE) prophylaxis post knee or hip replacement, more recently its use has been extended to include those patients requiring longer-term anticoagulation for treatment of VTE and non-valvular AF, and there is ongoing research into its use in other prothrombotic conditions.

Pharmacology

Figure 1 outlines the pharmacological action of rivaroxaban. It is an oxazolidinone derivative that binds selectively and reversibly to factor Xa, causing competitive inhibition of Xa and preventing thrombin formation. This has effects on platelet aggregation and fibrin formation but no direct effect on platelet function. Unlike indirect-Xa inhibitors such as fondaparinux, rivaroxaban inhibits both free and prothrombinase complex bound Xa.

Rivaroxaban is ingested in a fixed-dose oral formation with maximum plasma levels reached 2–4 hours following ingestion. It has a high oral bioavailability and at doses of up to 15mg shows predictable linear kinetics. It is metabolised by cytochrome

dependent and independent mechanisms and approximately one-third undergoes direct renal excretion. It is used therefore with caution in patients with renal impairment and is contraindicated in patients with a creatinine clearance of <15ml/min. The manufacturer advises against use in Child-Pugh B and C cirrhotic patients or liver disease with associated coagulopathy. Drug interactions can be problematic as a result of partial cytochrome dependent metabolism, but is not as restrictive as warfarin. The half-life of rivaroxaban varies from 5 to 13 hours depending on creatinine clearance.

As with any anticoagulant, use should be avoided in those prone to bleeding, including uncontrolled hypertension. There is no known antidote to rivaroxaban and so management of haemorrhage can be difficult. In minor bleeding, withholding rivaroxaban should be sufficient but blood products and prothrombin complex may be required in more severe bleeds.

Trials of safety and efficacy

The biggest study to date showing rivaroxaban as an effective alternative anticoagulant to warfarin in AF is the ROCKET AF study. This was a randomised double-blind trial involving 1178 centres across 45 countries, conducted with the aim of proving non-inferiority of rivaroxaban to warfarin in preventing thromboembolic phenomenon in patients with non-valvular AF. A total of 14 264 subjects were recruited with a $CHADS_2$ risk score of 2 or more, and assigned to rivaroxaban 20mg once daily (15mg if creatinine clearance 30–49ml/min) or warfarin targeting an INR of 2–3. Primary efficacy endpoints of stroke or other embolic disease and safety endpoint of significant haemorrhage were recorded. Non-inferiority was shown in both per-protocol as-treated analysis (1.7 events/100 patient years for the rivaroxaban group vs 2.2 for warfarin) and intention to treat analysis (2.1 vs 2.4), and was statistically significant ($p<0.001$). Overall rates of bleeding were similar in both groups. Rivaroxaban had lower rates of intracranial haemorrhage (hazard ratio 0.67, 95% CI 0.47–0.93) but higher rates of major gastrointestinal bleeding (3.2% vs 2.2%, $p<0.001$). Fatal bleeding occurred less frequently with rivaroxaban.[1]

The EINSTEIN-PE trial was designed to prove non-inferiority of rivaroxaban to standard warfarin treatment in acute pulmonary embolus (PE) and preventing recurrent VTE. In all, 4832 patients with symptomatic acute PE were randomised to either rivaroxaban (15mg twice daily for 3 weeks and 20mg daily thereafter) or standard enoxaparin followed by warfarin for 3, 6 or 12 months. Results suggest similar clinical efficacy (non-inferiority margin 2, $p=0.003$) and similar numbers of clinically relevant bleeding episodes, but with less major bleeding events in the rivaroxaban group (1.1% vs 2.2%, $p=0.003$).[2]

The ATLAS 2 study has been investigating the role of low-dose rivaroxaban in secondary prevention of acute coronary syndrome (ACS). This is a large phase II randomised trial comparing conventional therapy alongside twice-daily rivaroxaban or placebo in patients with ACS. Rivaroxaban significantly reduced death from cardiovascular causes, myocardial infarction or stroke compared with placebo (8.9% vs 10.7%, $p=0.008$), but had increased bleeding rates.[3]

Evidence specific to diabetes

There was no specific subgroup analysis for those with diabetes in ROCKET AF but they contributed to 40.4% and 39.5% of the rivaroxaban and warfarin groups, representing a large proportion of study numbers.[1] ATLAS 2 enrolled a reasonable number of diabetes patients also, across treatment and placebo groups (32.3%, 31.8%, 31.8%). Subgroup analysis for diabetes showed a slight reduction in the primary efficacy endpoint with rivaroxaban (7.1% vs 7.5%) but was not statistically significant.[3]

Discussion

Cardiovascular disease in diabetes has a significant burden on individual and population health, with a recent Scottish survey identifying devastating high prevalence of myocardial infarction (10.2%) and cerebrovascular disease (5.3%) in patients with type 2 diabetes.[4] This emphasises the need for optimal anticoagulation in higher risk individuals within this group who have identified prothrombotic disease.

Key points

- The prevalence of atrial fibrillation (AF) is higher in those with diabetes, giving a five-fold increase in incidence of stroke
- Rivaroxaban, the first oral direct inhibitor of factor Xa, has been shown to have equivalent efficacy and similar safety profile as warfarin for prevention of thromboembolic events in AF and in the treatment of pulmonary embolism, but without the need to monitor
- Rivaroxaban has also been shown to be effective when used for thromboprophylaxis and in the treatment of acute coronary syndrome

ROCKET AF showed non-inferiority of rivaroxaban compared with warfarin in preventing stroke and suggested a similar safety profile, perhaps with lower risks of intracranial bleeding. Over 90% of the study population had a $CHADS_2$ score of ≥3, which is higher than a lot of the patients we would currently anticoagulate in practice.[1] Evidence should, however, be transferrable to lower risk groups. On this basis, both NICE and the Scottish Medicine Consortium (SMC) have accepted it as an alternative to warfarin in patients with AF, with the SMC restricting use to patients intolerant of coumarins or with a 'labile' INR. It also has approval from SMC and NICE for treatment of DVT and initial data in ACS look promising.

With any new therapy, cost effectiveness is vital, particularly under the constraints of the NHS budget. It is difficult to establish exact costs of warfarin treatment given patient variability, but it is possible that rivaroxaban will offer a cost-effective alternative.

Like rivaroxaban, there is evidence to support non-inferiority of dabigatran compared with warfarin and LMWH in the conditions discussed. There is, however, a lack of evidence to compare direct-Xa and thrombin inhibitors and, while hypothesised conclusions can be drawn from pre-existing studies, it is difficult to establish superiority of one over the other.

Declaration of interests

There are no conflicts of interest.

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References are available online at www.practicaldiabetes.com.

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