Apixaban

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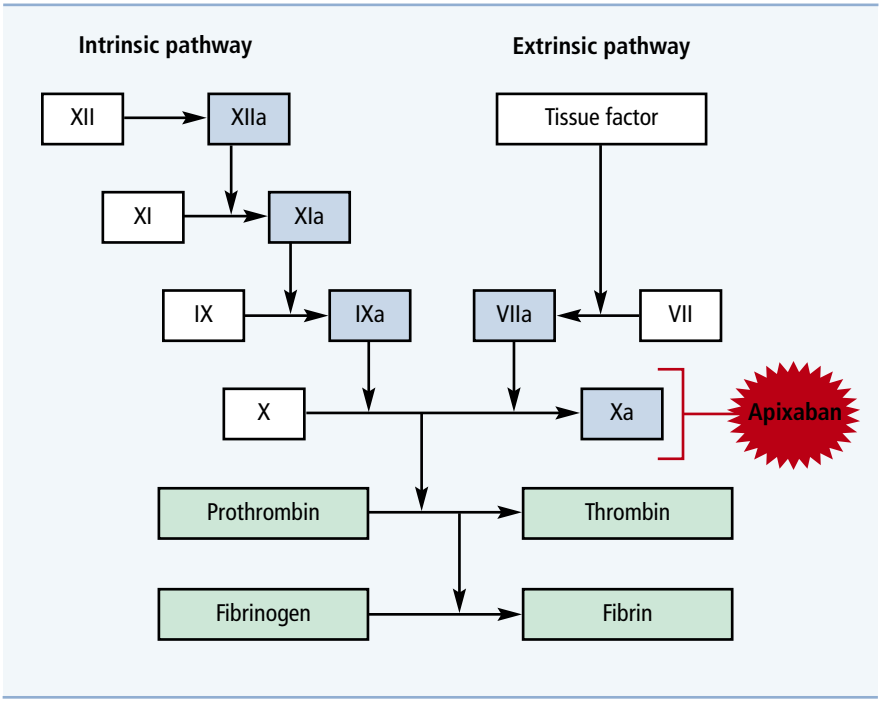

Figure 1. Apixaban is a highly selective, potent and direct inhibitor of factor Xa. It functions by inhibiting factor Xa, which inhibits thrombin generation and ultimately thrombus formation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with thromboembolic events. AF is responsible for a 5-fold increase in stroke risk and accounts for around 15% of all strokes. Stroke is associated with considerable morbidity and mortality. The common risk factors for AF are cardiovascular, including diabetes mellitus, and they are involved in the development and progression of AF. However, diabetes mellitus may also be an independent risk factor for both AF and thromboembolic events. The precise pathogenic mechanisms are unclear but may be related to autonomic, structural and electrical remodelling as well as insulin resistance. The longer the history of diabetes, or the higher the HbA_{1c}, the higher the risk of AF.[1]

Anticoagulation is used to reduce the stroke risk and associated morbidity. Warfarin is a vitamin K antagonist and is historically the mainstay of treatment. However, there are many associated problems, including unpredictable pharmacokinetics due to genetic polymorphisms in metabolising enzymes, a narrow therapeutic range requiring frequent blood monitoring, potential food and drug interactions and serious adverse events including intracerebral haemorrhage. Therefore the production of new oral anticoagulants with more predictable outcomes has been highly anticipated. Apixaban is a factor Xa inhibitor that has been licensed for use in the UK for prophylaxis of stroke and systemic embolism in patients with non-valvular AF and at least one risk factor such as previous stroke or transient ischaemic attack, symptomatic heart failure, diabetes mellitus, hypertension, or age ≥75 years. It is also licensed for the prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery. Research studies have also shown efficacy and safety in the treatment of venous thromboembolism.

Pharmacology

Figure 1 outlines the pharmacological action of apixaban. It is a highly selective, potent and direct inhibitor of factor Xa. It functions by inhibiting factor Xa, which inhibits thrombin generation and ultimately

thrombus formation. Apixaban inhibits free and prothrombinase complex bound FXa, and prothrombinase activity. It has no direct effect on platelets but indirectly inhibits platelet aggregation and fibrin formation induced by thrombin.

Apixaban is taken orally, has >50% bioavailability, and reaches peak plasma concentration in 3–4 hours. The half life is 10–14 hours after repeated doses, and reaches steady state plasma concentrations in 72 hours. It is metabolised in the liver via CYP3A4 and CYP-independent mechanisms. Apixaban exhibits a dual mechanism of excretion with approximately 25% appearing in urine and the remainder in faeces. The presence of multiple elimination pathways means that patients with renal or hepatic impairment may still be managed with apixaban. It is not thought to inhibit or induce cytochrome enzymes and therefore has a low risk of drug interactions.

Apixaban prolongs the INR and APTT in a concentration dependent manner. However, this effect is minimal at therapeutic concentrations. Although monitoring is not required routinely, the assessment of drug levels may be required in certain circumstances, e.g. bleeding complications, emergency surgery or in overdose. In these cases, anti-Xa levels were shown to be reliable indicators of apixaban concentration.

Trials of safety and efficacy

There have been two major randomised, double-blind trials evaluating the effectiveness and safety of apixaban in atrial fibrillation. The double-blind AVERROES study randomly assigned 5599 patients to 5mg apixaban twice daily or aspirin (varied dose 81–324mg) in warfarin intolerant patients.[2] The primary objective was to determine whether apixaban was superior to aspirin at preventing stroke or systemic embolism in AF. The event rate was significantly reduced from 3.7%/year in the aspirin group to 1.6%/year in the patients treated with apixaban (p<0.001). The trial was stopped early due to interim analysis showing a significant reduction in stroke with a mean follow up of 1.1 years. There was no increase in major bleeding rates between groups.

ARISTOTLE was a randomised, double-blind trial comparing apixaban (at a dose of 5mg twice daily) with warfarin (target international normalised ratio, 2.0 to 3.0) in 18 201 patients with atrial fibrillation and at least one additional risk factor for stroke.[3] The primary outcome was ischaemic or haemorrhagic stroke or systemic embolism. Results demonstrated that apixaban was superior to warfarin in reducing stroke and systemic embolism with 212 subjects and 265 subjects respectively (1.27% vs 1.60%, p=0.01) reaching the primary outcome. Apixaban also showed significantly fewer major bleeds (2.13% and 3.09% in warfarin, p<0.001) and a lower rate of cardiovascular death. Non-vascular death rates were comparable between groups.

Specific evidence for use in diabetes

Although 19% of patients in the AVERROES study had diabetes, a subgroup analysis was not reported. In the ARISTOTLE trial, 25% of patients had diabetes and the reduction in primary outcome was also seen for this and other subgroups. The risk of bleeding was reduced comparing apixaban with warfarin in non-diabetic subjects from 3.1%/year with warfarin to 1.9%/year with apixaban, but in people with diabetes the bleeding rates were similar for apixaban and warfarin at 3.1%/year with warfarin and 3.0% with apixaban, and this interaction was statistically significant.

Discussion

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes, with a 2- to 4-fold increase in risk. This includes an increased risk of AF, which is associated with thromboembolic disease and stroke with significant morbidity and mortality. It is important to consider anticoagulation in these patients to prevent this potentially disabling or fatal outcome.

Apixaban is a new oral factor Xa inhibitor that has been shown to be more effective than warfarin in reducing stroke and systemic thromboembolism in patients with non-valvular AF, as well as being associated with reduced adverse outcomes including a lower risk of bleeding.

Key points

- Atrial fibrillation and thromboembolic disease are more common in patients with diabetes
- Apixaban is an oral factor Xa inhibitor that has been shown to be more effective than warfarin at preventing thromboembolic stroke including in patients with diabetes
- Apixaban has a better side effect profile and may be as cost-effective as warfarin, without the need for monitoring

Other advantages of apixaban over warfarin include fewer drug and food interactions, no requirement for monitoring, and stable reproducible anticoagulation effects. Apixaban in addition to other newer anticoagulants will challenge the place of warfarin as the first-line choice for patients with AF. How quickly the move away from warfarin will happen will depend on cost.

Cost-effectiveness is an important consideration with apixaban costing £2.20 daily, with an annual cost of £803. This is compared to £0.12 daily for warfarin and annual INR monitoring cost of £248 (NICE).[4] However, the reduction of adverse events must be taken into consideration, especially the reduction in risk of intracranial haemorrhage. NICE concluded that apixaban was cost-effective compared with warfarin, with the incremental cost-effectiveness ratio (ICER) being <£20 000 per quality-adjusted life years (QALY) gained.

Apixaban is currently licensed for use within the UK and approved by NICE as an option for patients with non-valvular AF and an additional risk factor. Given that one of the risk factors is diabetes, it is likely that many patients in this population may benefit.

Declaration of interests

RL has no conflict of interest. MF has received payments for lectures and advisory boards from BMS and Pfizer for other products. GMcK has done advisory board and consultancy work for BMS and Pfizer for apixaban (for treatment of VTE).

References

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