Apixaban: new anticoagulant for stroke prevention

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Apixaban is a new oral anticoagulant licensed for the prevention of stroke and systemic embolism. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse events compared with warfarin and aspirin, and hospital specialists discuss its place in stroke prevention.

The 2006 NICE guideline on the management of atrial fibrillation (AF) recommends warfarin as the antithrombotic of choice to prevent stroke.1 Subsequent technology appraisals have recommended dabigatran (Pradaxa)2 and rivaroxaban (Xarelto)3 as alternatives to warfarin (with slight differences, the risk factors defining treatment eligibility). Recent NICE guidance also recommends apixaban (Eliquis) as an option for preventing stroke and systemic embolism in people with nonvalvular AF with risk factors.4

The technology
Apixaban is, like rivaroxaban, a factor Xa inhibitor (dabigatran is a direct thrombin inhibitor). Unlike warfarin, none of these newer anticoagulants requires monitoring. Apixaban is licensed for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF with one or more risk factors (eg prior stroke or transient ischaemic attack, age ≥75 years, hypertension, diabetes mellitus or symptomatic heart failure).

Clinical trials
Apixaban has been compared with warfarin in patients with AF and at least one

KEY POINTS

- Apixaban is a factor Xa inhibitor for the prevention of stroke and systemic embolism in adults with nonvalvular atrial fibrillation with one or more risk factors for stroke.
- A month’s treatment at the recommended dose of 5mg twice daily costs £61.50.
- It is noninferior, and probably superior, to warfarin in preventing stroke or systemic embolism.
- It is superior to aspirin in preventing stroke or systemic embolism in patients for whom warfarin is inappropriate.
- It is associated with a lower risk of major and clinically relevant nonmajor bleeding than warfarin but not aspirin.
- Apixaban increases the choice of oral anticoagulants as an alternative to warfarin in the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and other risk factors.
NEW PRODUCTS | Apixaban

There have been significant developments in the management of stroke over the last two decades, though it remains a devastating condition. It carries significant morbidity and mortality and is a major cardiovascular challenge. Stroke is currently the third largest cause of death and the single largest cause of adult disability in England. More than 900,000 people are currently living with the effects of stroke, and half are dependent on others for help with activities of daily living. Stroke has an estimated cost to the economy of £7 billion a year, with a direct cost to the NHS of £2.8 billion.

Apixaban was greater in patients with prior stroke or transient ischaemic attack (2.5 vs 8.3 per cent per year). Fewer patients discontinued apixaban than warfarin (25.3 vs 27.5 per cent, \(p=0.001\)) or aspirin (17.9 vs 20.5 per cent, \(p=0.03\)).

### Adverse effects

Apixaban was associated with a significantly lower incidence of major bleeding and clinically relevant nonmajor bleeding than warfarin but not aspirin (see Table 1). The net clinical outcome of stroke, systemic embolism, major bleeding and death from any cause was significantly lower with apixaban than warfarin (6.13 vs 7.20 per cent per year, \(p<0.001\)) and (for stroke, systemic embolism, MI, death from vascular causes and major bleeding) aspirin (5.3 vs 7.2 per cent per year, \(p=0.003\)).

### Place in therapy

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### Table 1. Principal efficacy and safety end-points (per cent per year) in the ARISTOTLE and AVERROES trials

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE apixaban</th>
<th>warfarin</th>
<th>AVERROES apixaban</th>
<th>aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke or systemic embolism</strong></td>
<td>1.27a</td>
<td>1.60</td>
<td>1.66c</td>
<td>3.70</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1.19a</td>
<td>1.51</td>
<td>1.66c</td>
<td>3.40</td>
</tr>
<tr>
<td><strong>Haemorrhagic stroke</strong></td>
<td>0.24a</td>
<td>0.47</td>
<td>0.22a</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>3.53a</td>
<td>3.94</td>
<td>3.52f</td>
<td>4.40</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>2.13f</td>
<td>3.09</td>
<td>1.44f</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>major or clinically relevant nonmajor</td>
<td>clinically relevant nonmajor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.07c</td>
<td>6.01</td>
<td>3.18c</td>
<td>2.70</td>
</tr>
</tbody>
</table>

\( ^{a} \text{primary end-point} \quad ^{b} \text{p}=0.01 \quad ^{c} \text{p}<0.001 \quad ^{d} \text{p}=0.047 \quad ^{e} \text{p}=0.45 \quad ^{f} \text{p}=0.07 \quad ^{g} \text{p}=0.57 \quad ^{h} \text{p}=0.035 \)

### References


### Declaration of interests

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.
in people aged 80–89.\(^4\) Mortality from Af-related strokes is almost double that of other strokes and functional deficits are more likely to be severe.\(^5\) It is therefore vital that when Af is detected, appropriate management is initiated to reduce the risk of thromboembolic events.

**Warfarin**

The CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASC\(_6\) risk score systems are validated tools for individual risk stratification, and should be used to guide decisions regarding the need for anticoagulation in Af, along with open discussion with the patient. Where anticoagulation is indicated, warfarin offers cost-effective stroke prevention with a relative risk reduction of 62 per cent and a reduction in all-cause mortality of 26 per cent versus control.\(^7\)

Warfarin therapy does, however, have disadvantages. It requires monitoring of INR and regular blood tests, and efficacy is strongly dependent on time in therapeutic range. The above factors, combined with fears regarding bleeding, lead to high rates of discontinuation. Many physicians remain reticent to recommend warfarin in older patients, despite evidence that they benefit more than younger counterparts.\(^8\)

**Apixaban**

In recent years a number of alternative drugs have become available. Dabigatran, rivaroxaban and apixaban have all shown noninferiority to warfarin in the prevention of stroke and systemic emboli.\(^9\)–\(^11\) Their advantages are ease of use, predictable anticoagulant effects, low propensity for food and drug interactions, and lower rates of intracranial bleeding than with warfarin.\(^12\)

As detailed above, in the ARISTOTLE trial apixaban showed superiority (secondary end-point) over warfarin in preventing stroke or peripheral thromboembolism. This was primarily driven by a reduction in haemorrhagic stroke, with ischaemic stroke rates similar in the two groups. There was also less major bleeding and lower mortality.\(^11\) In the AVERROES study, apixaban showed superiority to aspirin in preventing stroke and systemic emboli with similar bleeding rates.\(^13\)

Apixaban does not require monitoring or regular blood tests and is well tolerated. In the ARISTOTLE study discontinuation was less frequent with apixaban compared to warfarin.\(^15\)

There are no direct data comparing apixaban with dabigatran or rivaroxaban, though indirect comparisons suggest similar efficacy with reduced rates of major and minor bleeding. More robust data are required to draw any firm comparisons.\(^14\)–\(^16\)

Recent NICE and European Society of Cardiology (ESC) guidelines recommend apixaban as a treatment option to prevent stroke and systemic embolism in people with nonvalvular Af.\(^5\)–\(^17\) Apixaban is cost effective when compared to warfarin with an annual cost of £803, similar to rivaroxaban and dabigatran.\(^18\),\(^19\)

Despite a reduction in bleeding rate with apixaban compared to warfarin, it is important to note that there is no available antidote and no reliable laboratory assay.

**Conclusion**

Direct thrombin and factor Xa inhibitors are an exciting development in the prevention of stroke and systemic emboli in Af. They may replace warfarin in many patients with Af due to convincing data both on efficacy and safety as well as convenience. However, challenges remain with respect to lack of specific antidotes and higher costs.

Those well established on warfarin with good INR control are unlikely to derive significant benefit by switching agents. Apixaban is superior to aspirin in stroke prevention for those unable to take warfarin, with a similar bleeding risk and thus may have an additional niche in the market.

There is a lack of data to directly compare the new oral anticoagulants and a need for more research into the management of bleeds for patients taking these drugs.

**References**


**Declaration of interests**

Dr Manning and Dr Lam: none to declare; Professor Robinson has received advisory board payments from Boehringer Ingelheim and Daiichi Sankyo.

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