Properties and use of novel oral anticoagulants

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Steve Chaplin and Dr Washik Parkar provide an overview of the properties of novel oral anticoagulants and how they compare in stroke prevention in AF.

There are currently three novel oral anticoagulants (NOACs) available: apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto). Apixaban and rivaroxaban are direct inhibitors of activated factor X, whereas dabigatran is a direct inhibitor of thrombin. They appear to be equally effective.

They have simple dose regimens and do not require dose titration. They are taken orally, are not associated with drug interactions and their activity is unaffected by diet, so there is no need to monitor coagulation. In that way they are more convenient than either heparin or warfarin and they relieve patients of the anxiety of bleeding complications when INR is difficult to stabilise during warfarin therapy.

NOACs are also associated with a lower risk of intracranial bleeding than warfarin, though the overall risk of major bleeding events is similar.

The transition from warfarin to prescribing NOACs has not been as brisk as these advantages might suggest. Warfarin may be difficult to use but it is cheaper and familiar, and monitoring services are well established. When INR is in the target range, it is effective and well tolerated.

Unlike the NOACs, warfarin has an antidote. Further, uptake of the NOACs was delayed while NICE prepared guidance on their use; now they have all been recommended in each of the appraised indications.

Indications
All the NOACs are licensed for the prevention of venous thromboembolic events in adults who have undergone elective hip and knee replacement surgery.

They are also indicated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) who have one or more risk factors (such as diabetes mellitus, coronary artery disease or hypertension). The precise wording of the licensed indications varies slightly but how this affects prescribing is unknown.

Rivaroxaban is the only NOAC licensed for the treatment of DVT and pulmonary embolism and prevention of recurrent DVT and PE.

NICE guidance
All three NOACs are recommended by NICE as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. They are also recommended as an option for preventing stroke and systemic
embolism in people with nonvalvular AF with one or more risk factors, though the wording of the guidance reflects the small differences in the product licences.

NICE adds that the decision to start treatment should be made after an informed discussion between the clinician and the patient about the risks and benefits compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to a NOAC should be considered in light of their INR because the NOACs are not superior when INR is in the target range.

NICE also recommends rivaroxaban as an option for treating DVT and preventing recurrent DVT and PE in adults who have been diagnosed with acute DVT.

**Dose and dose adjustment**

The NOACs should not be considered a homogeneous group. About 85 per cent of dabigatran is excreted renally compared with a third of rivaroxaban and a quarter of apixaban. Conversely, hepatic metabolism is greatest for rivaroxaban – two-thirds of the dose compared with 20–25 per cent for the other NOACs.

### Drug Points

**NOACs**

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Dose</th>
<th>Duration</th>
<th>Dose reduction</th>
<th>Basic cost at standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee or hip replacement</strong></td>
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<tr>
<td>apixaban</td>
<td>2.5mg twice daily, starting 12–24 hours after surgery</td>
<td>hip: 32–38 days knee: 10–14 days</td>
<td>no dose adjustment; caution in severe renal impairment and mild/moderate hepatic impairment; contraindicated in severe hepatic impairment</td>
<td>hi: £70.29–£83.47 knee: £21.97–£30.75</td>
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<tr>
<td>dabigatran</td>
<td>first dose 110mg within 1–4 hours of completed surgery then 220mg once daily</td>
<td>hip: 28–35 days knee: 10 days</td>
<td>reduce to 75mg once daily in patients with moderate renal impairment; treatment with verapamil, amiodarone or quinidine; age ≥75</td>
<td>hi: £61.51–£76.88 knee: £21.97</td>
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<tr>
<td>rivaroxaban</td>
<td>10mg within 6–10 hours of surgery, then 10mg once daily</td>
<td>hip: 35 days knee: 14 days</td>
<td>no dose adjustment (caution in severe renal impairment; contraindicated in hepatic disease with increased bleeding risk)</td>
<td>hi: £73.50 knee: £29.40</td>
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<tr>
<td><strong>Atrial fibrillation</strong></td>
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<tr>
<td>apixaban</td>
<td>5mg twice daily</td>
<td>long term</td>
<td>reduce to 2.5mg twice daily in patients with at least 2 of the following: age ≥80 years, body weight ≤60kg, serum creatinine ≥1.5mg/dl (133µmol/l)</td>
<td>£61.51 per 28 days</td>
</tr>
<tr>
<td>dabigatran</td>
<td>150mg twice daily</td>
<td></td>
<td>110mg twice daily if age ≥80 or concomitant verapamil 110–150mg twice daily depending on risk for age 75–80; moderate renal impairment; gastritis, gastro-oesophageal reflux or oesophagitis; increased bleeding risk</td>
<td>£61.51 per 28 days</td>
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<tr>
<td>rivaroxaban</td>
<td>20mg once daily</td>
<td></td>
<td>moderate/severe renal impairment: 15mg once daily; contraindicated in hepatic disease with increased bleeding risk</td>
<td>£58.80 per 28 days</td>
</tr>
<tr>
<td><strong>Treatment and secondary prevention of DVT/PE</strong></td>
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<tr>
<td>rivaroxaban</td>
<td>15mg twice daily for 21 days then 20mg once daily</td>
<td>3 months if risk factors transient, otherwise clinical judgement</td>
<td>moderate/severe renal impairment: consider reducing long-term dose to 15mg once daily depending on risk of bleeding</td>
<td>£88.20 then £58.80 per 28 days</td>
</tr>
</tbody>
</table>

**Figure 1.** Dosage regimens and cost of currently available NOACs
Dosing is more straightforward than for warfarin and requires little or no adjustment for some patients but, for those taking other drugs or in whom clearance may be reduced, prescribing recommendations differ by drug and by indication (see Table 1).

For dabigatran, renal function should be assessed before use and, for patients taking long-term therapy, annually thereafter. Patients with oesophagitis, gastritis or gastroesophageal reflux are at increased risk of bleeding during treatment with dabigatran and should be given a reduced dose.

**Drug interactions**

Hepatic metabolism of the NOACs depends on the efflux transporter P-glycoprotein and, except for dabigatran, hepatic CYP3A4 enzymes. Strong inducers or inhibitors of these systems should not be co-administered; examples include rifampicin, some protease inhibitors, azole antifungals such as itraconazole and St John’s wort. However, several drugs have more modest effects or affect only one of these systems and may be used with caution; examples include clarithromycin, diltiazem and verapamil.

Drugs that increase bleeding risk, such as antithrombotics, NSAIDs and the SSRIs, may have additive effects with the NOACs and treatment should be closely monitored.

Recommendations on the use of concomitant drug therapy differ between the NOACs (eg carbamazepine should be avoided with dabigatran but may be used with caution with apixaban and rivaroxaban) and the risk associated with drug interactions is influenced by a patient’s other risk factors. The safety of multiple drug therapy should therefore be checked for each individual.

**Adverse effects**

As is the case with warfarin, safety concerns focus on the risk of bleeding but the NOACs have been associated with adverse gastrointestinal effects. All may cause nausea, but dyspepsia is associated with dabigatran and rivaroxaban and gastro-esophageal reflux with dabigatran only. Other gastrointestinal events include diarrhoea, constipation and abdominal pain.

**Declaration of interests**

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

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**Place in therapy**

The NOACs have been developed to overcome the shortcomings of warfarin for stroke prevention in AF. Warfarin’s narrow therapeutic index makes it difficult to maintain patients within a defined anticoagulation range. The problem is further compounded by the fact that individual dosage requirements vary widely between and within individuals, which adds to the inconvenience to patients.

These drugs have a rapid onset and offset of action without the need for routine anticoagulation monitoring. They have fixed dosing with few drug or dietary interactions.

Recommendations for the use of NOACs are included in current European guidelines and all three NOACs are recommended by NICE as an alternative to warfarin.

Clinical studies have demonstrated that all three currently licensed NOACs are not inferior to warfarin in the prevention of systemic embolus and stroke. However, dabigatran 150mg and apixaban 5mg were found to be superior. All three demonstrated a reduction in intracranial haemorrhage.

Patients receiving dabigatran 110mg and apixaban 5mg daily experienced less bleeding while rivaroxaban 20mg and dabigatran 150mg did not differ compared to warfarin.

In daily practice NOACs are appropriate for a number of patients groups including those who are naive to or intolerant of warfarin or if warfarin is contraindicated. However warfarin is still widely used in patients with valvular heart disease and prosthetic heart valves.

NOACs have a particular advantage over warfarin if the TTR (time in therapeutic range when the INR is between 2 and 3) cannot be maintained. The choice of NOAC and dosing regimen is vital in routine practice and decision aids can help the prescriber to decide which to use and to become familiar with its nuances.

**References**


**Declaration of interests**

Dr Parkar has received honoraria from Servier, BMS, Pfizer, Boehringer-Ingelheim and Bayer.

Dr Parkar is a GP with specialist interest in cardiology and clinical lead primary care, North Manchester CCG

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**Letters**

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