Thrombotic disease is the most common cause of morbidity and mortality worldwide. It encompasses several clinical conditions including ischaemic heart disease, stroke and venous thromboembolism. Vitamin K antagonists (VKAs), such as warfarin, have formed the cornerstone of anticoagulation therapy for the prevention and treatment of thromboembolic disease for over 60 years. Warfarin is an effective oral preparation for long-term anticoagulation, but it does have significant limitations. It has high interindividual variability in an unpredictable dose-response relationship that requires monitoring by laboratory testing, as well as numerous drug and food interactions.

Over the past few years, the clinical burden of thromboembolic disease and the limitations of current therapies have prompted the development of orally administered alternatives to VKAs called direct oral anticoagulants (DOACs). Previously known as ‘novel oral anticoagulants (NOACs)’, DOACs are direct and specific inhibitors of single coagulation factors and have the significant advantage over warfarin of not requiring coagulation monitoring. To date, four DOACs have been approved and licensed: dabigatran, which inhibits thrombin (factor IIa); and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban.

**Indications for anticoagulation**

Table 1 summarises the current UK licensed indications for each DOAC, along with dosing details and adjustment requirements. There are several clinical conditions in which anticoagulation has been shown to be beneficial, but in general terms, it is used for either primary or secondary prevention of venous or arterial thrombotic events. Venous thromboembolism and prevention of stroke in atrial fibrillation are the most common indications for anticoagulation, and are discussed in more detail below.

**Venous thromboembolism**

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), has a clinical incidence of approximately 1.1–1.8 per 1000 adults annually, with slightly higher rates in men. Two-thirds of cases present as DVT and one-third as PE with or without DVT. The major outcomes of VTE are death, recurrence, post-thrombotic syndrome, pulmo-
nary hypertension, and anticoagulation-induced major bleeding. The mortality rate for PE is difficult to assess as it is often unrecognised before death, but it has been estimated at 17 per cent at three months in a population-based study.\(^2\) There is a strong association with increasing age, which clearly has major implications for healthcare systems in our ageing population.\(^1\)

Duration of anticoagulation in VTE is a controversial area. Although there is agreement on the minimum length of time a patient with first VTE (provoked or unprovoked) should be treated (three months), the optimal length of time is not known. Certain patient groups may benefit from extended anticoagulation to 6 or 12 months, eg those with a persistent but reversible risk factor, and some patients should be considered for indefinite anticoagulation, eg recurrent VTE, unprovoked proximal DVT and symptomatic PE.

### Stroke prevention in nonvalvular atrial fibrillation

<table>
<thead>
<tr>
<th>Class</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IIa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

### Acute venous thromboembolism treatment

<table>
<thead>
<tr>
<th>Licensed in UK?</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Phase 3 trial</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
</tr>
</thead>
</table>

| Dosage adjustments | 110mg twice daily if concomitant verapamil; consider reduction to 110mg twice daily if high bleeding risk or CrCl 30–50ml/min | 15mg daily if CrCl 15–49ml/min | 2.5mg twice daily if CrCl 15–29ml/min, or if creatinine ≥133µmol/L and age ≥80 years or body weight ≤60kg | 30mg daily if one or more of: CrCl 15–50ml/min, weight <60kg or concomitant ciclosporin, dronedarone, erythromycin or ketoconazole |
| Dosage           | 150mg twice daily (18–74 years); 110–150mg twice daily (75–79 years); 110mg twice daily (≥80 years) | 20mg daily | 5mg twice daily (18–79 years); 2.5mg twice daily (≥80 years) | 60mg daily |
| Dosage adjustments | Consider reducing to 110mg twice daily if increased bleeding risk and CrCl 30–50ml/min; reduce to 110mg twice daily if concomitant verapamil | Consider reducing to 15mg daily if CrCl 15–49ml/min and excess bleeding risk | N/A | 30mg if one or more of: CrCl 15–50ml/min, weight <60kg or concomitant potent P-gp inhibitor |

### Table 1. UK licensing and dosing information for direct oral anticoagulants

Symptomatic PE. Its prevalence increases with age, with current estimates of 1.5–2 per cent expected to at least double in the next 50 years as the population ages.
The rate of ischaemic stroke among patients with nonvalvular AF averages 5 per cent per year; two to seven times that of people without AF. Stroke in AF is often severe and can cause death or long-term disability, resulting in a sizable burden on health resources. An individual’s predisposition to stroke in AF is related to a number of well-documented risk factors – age, hypertension, prior stroke or transient ischaemic attack (TIA), diabetes and structural heart disease.

The identification of these risk factors has led to the development of a stratification algorithm called the CHA2DS2-VASc score. Current NICE guidance is that any patient with a score of 2 or more should receive anticoagulant therapy, and those with a score of 1 should be considered for anticoagulation, taking bleeding risk into account.4 There are bleeding risk models available, such as HAS-BLED, which take into account clinical and demographic patient characteristics known to increase bleeding on anticoagulants.5 They may assist the clinician in balancing the risk and benefit of anticoagulant therapy, but it should be remembered that many risk factors for stroke in AF are also risk factors for bleeding.

DOACs have been approved for stroke prevention in nonvalvular AF. The distinction between valvular and nonvalvular AF is a matter of significant debate, and even the large DOAC clinical trials differed in their exclusion criteria for patients with valvular disease. However, the current most widely accepted definition of valvular AF is those patients with mitral stenosis or artificial heart valves, and these patients should receive warfarin instead of a DOAC.6

### Other indications
DOACs have also been investigated and approved for use in VTE prophylaxis in major orthopaedic surgery. Their role in the treatment of acute coronary syndromes (ACS), in conjunction with antiplatelet agents, remains under investigation. To date, only rivaroxaban has been licensed in Europe for secondary prevention in stabilised ACS patients who presented with elevated cardiac biomarkers, in combination with antiplatelet therapy.7

DOACs have not been approved for patients with mechanical heart valves. Dabigatran was found to cause excess thromboembolic and bleeding events compared with warfarin in patients with mechanical valves, and the factor Xa inhibitors have not been studied in this setting.8

### Mechanism of action
All DOACs block major procoagulant activities involved in the generation of a fibrin clot, by directly inhibiting either factor Xa or thrombin (see Figure 1).

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary venous thromboembolism prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed in UK?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phase III trial</td>
<td>RE-MEDY/RE-SONATE</td>
<td>EINSTEIN-EXT</td>
<td>AMPLIFY-EXT</td>
<td>HOKUSAI-VTE</td>
</tr>
<tr>
<td>Dosage</td>
<td>150mg twice daily after LMWH</td>
<td>20mg daily</td>
<td>2.5mg twice daily</td>
<td>60mg daily</td>
</tr>
<tr>
<td>Dosage adjustments</td>
<td>As per acute venous thromboembolism treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Venous thromboembolism prophylaxis in major orthopaedic surgery** |            |             |          |          |
| Licensed in UK?        | Yes        | Yes         | Yes      | No       |
| Phase 3 trial          | RE-MOBILIZE, RE-MODEL, RE-NOVATE, RE-NOVATE-II | RECORD 1 TO 4 | ADVANCE 1 TO 3 | STARS J5 |
| Dosage                 | 110mg first dose, then 220mg daily | 10mg daily | 2.5mg twice daily | N/A      |
| Dosage adjustment      | 75mg first dose then 150mg daily if any of: CrCl 30–50ml/min, age ≥75 years, concomitant potent P-gp inhibitor | N/A | N/A | N/A |

CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; P-gp = P-glycoprotein

Table 1. UK licensing and dosing information for direct oral anticoagulants (cont.)
**Dabigatran – a direct thrombin inhibitor**

Thrombin (factor IIa) is the final enzyme of the clotting cascade that produces fibrin; it is formed by the proteolytic cleavage of prothrombin by factor Xa.

Dabigatran is a selective thrombin inhibitor given as dabigatran etexilate (an orally available prodrug), as dabigatran itself is not absorbed from the gut. It is a synthetic molecule that prevents access to the active site on both free and clot-bound thrombin by forming a salt bridge via hydrophobic interactions. The half-life is approximately 12 to 17 hours in individuals with normal renal function, and absorption is unaffected by food. Dabigatran capsules should only be dispensed and stored in the original packaging and not stored in pill boxes or organisers, to prevent breakdown from moisture and loss of potency. Dabigatran can be directly reversed by idarucizumab, a humanised dabigatran-specific monoclonal antibody given intravenously as two separate 2.5g doses no more than 15 minutes apart.

**Rivaroxaban, apixaban and edoxaban – factor Xa inhibitors**

Rivaroxaban, apixaban and edoxaban share a common mode of action. They are direct competitive inhibitors of factor Xa, reversibly binding to the factor Xa active site and preventing generation of new thrombin molecules.

Apixaban and edoxaban can be taken without food, but higher doses of rivaroxaban (>15mg) should be taken with food to allow complete absorption. Approximate half-lives are as follows: rivaroxaban 7–17 hours, apixaban 5–9 hours and edoxaban 6–11 hours.

**Once-daily versus twice-daily dosing**

The issue of once or twice-daily dosing of DOACs is a contentious one, as many have wondered why rivaroxaban can be given once daily for stroke prevention in AF whereas apixaban and dabigatran are given twice daily, despite the drugs having similar half-lives. Determining the optimum drug dosing regimen requires consideration of more than simply drug half-life, involving evaluation of the peak and trough drug levels obtained and the balance between efficacy and bleeding.

Phase 2 clinical trials of rivaroxaban found no clear advantage of twice-daily dosing over once-daily dosing, and therefore it was the once-daily dosing regimen that was

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**Figure 1.** Anticoagulant drugs and their targets in the coagulation process. Red dotted lines denote inhibition of clotting factors by each anticoagulant. VKA = vitamin K antagonist
Comparison with warfarin

Table 2. Comparison of warfarin with direct oral anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Many</td>
<td>Some interaction with CYP3A4 and P-glycoprotein inhibitors (see main text)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once daily</td>
<td>May require twice daily (apixaban, dabigatran)</td>
</tr>
<tr>
<td><strong>Dietary restrictions</strong></td>
<td>Requires consistent level of vitamin K intake</td>
<td>None</td>
</tr>
<tr>
<td><strong>Onset/offset of action</strong></td>
<td>Slow</td>
<td>Quick – removes need for heparin bridging and simplifies periprocedural management</td>
</tr>
<tr>
<td><strong>Reversal agents</strong></td>
<td>Well-established, effective reversal agents (vitamin K, prothrombin complex concentrates)</td>
<td>Idarucizumab for dabigatran. No reversal agent currently licensed for factor Xa inhibitors (but in development)</td>
</tr>
<tr>
<td><strong>Dependence on renal function</strong></td>
<td>None</td>
<td>Contraindicated in severe renal failure</td>
</tr>
</tbody>
</table>

The DOACs differ from VKAs such as warfarin in several ways (see Table 2), and these differences should be taken into account at the individual patient level when deciding on anticoagulation therapy.

The rapidity of onset and shorter half-life of the DOACs has significant advantages in the acute setting, in that bridging with parenteral anticoagulants when initiating therapy is not required in most situations. In the situation of an elective procedure with high bleeding risk, DOACs can be stopped two to three days before the surgery – in contrast to warfarin, which should be stopped at least five days prior to the procedure and may require ‘bridging’ with low-molecular-weight heparin (LMWH). Postoperatively, DOACs should be restarted once haemostasis has been achieved, but it should be remembered that full anticoagulant effect will occur within hours and therefore problems with bleeding could occur if started too early.

For many patients, the lack of drug and food interactions with DOACs compared with warfarin is a significant advantage, as is the lack of requirement for routine monitoring. There are also potential healthcare economic advantages conferred by the lack of monitoring required, as traditionally, large anticoagulant clinics have been required to manage VKA monitoring. However, it should be remembered that international normalised ratio (INR) monitoring can be of use in monitoring compliance with anticoagulation, as well as being a surrogate marker for adherence to other therapies.

Despite their many advantages over warfarin, the DOACs do have some limitations. Dabigatran and apixaban are dosed twice daily whereas warfarin is once daily. DOACs are renally excreted, therefore they must be prescribed with caution in renal dysfunction and are contraindicated in severe renal impairment (creatinine clearance <15ml/min). DOACs have variable and agent-dependent effects on routine coagulation tests, and although there are assays available to measure plasma drug concentrations, these are not widely available. Therefore, in the situation of major bleeding or emergency surgery, there is often no test available to accurately determine the amount of anticoagulant effect present. Similarly, in these situations, a further problem is the lack of reversal agent available for some DOACs. Idarucizumab has recently been approved for reversal of dabigatran, but at present there is no licensed reversal agent for the factor Xa inhibitors. However, there is an agent in development (andexanet alfa), which has shown promising results for reversal of rivaroxaban, apixaban and edoxaban.

Side-effects

The major side-effect of all anticoagulant therapy, regardless of class, is bleeding. Risk of bleeding with each individual DOAC in comparison with warfarin has been evaluated in large clinical trials. The overall risk of DOACs versus VKAs was reviewed in a meta-analysis of 12 randomised trials that included 102,607 patients with either AF or VTE. DOACs were associated with lower risks of major bleeding, fatal bleeding and intracranial bleeding, and major gastrointestinal bleeding was not increased. Of note, these data come from trials in which there was no antidote available for DOACs. Apart from gastrointestinal upset (11 per cent with dabigatran), nonhaemorrhagic side-effects are uncommon in DOACs.

Interactions

Apixaban and rivaroxaban are substrates for cytochrome p450 (CYP) isoforms, such as CYP3A4 and P-glycoprotein (P-gp). In view of this, concomitant treatment with systemic azole antifungtics or HIV protease inhibitors is not recommended as they will increase bleeding risk. For apixaban or rivaroxaban, concomitant use of less potent inhibitors of CYP3A4 and/or P-gp results in smaller increases in plasma anticoagulant concentrations, which are unlikely to be clinically relevant. Edoxaban elimination is only slightly dependent on CYP3A4 mechanisms and is mostly mediated by P-gp. Dabigatran is dependent on P-gp...
transporters but is not metabolised by CYP enzymes. Caution and dose adjustment are therefore required for dabigatran with the use of P-gp inhibitors and inducers.

Future development
Randomised clinical trials have stringent inclusion and exclusion criteria, and this should be considered when interpreting results as they may not be directly applicable to ‘real world’ clinical practice. This was an initial concern with DOACs, but postmarketing observational studies suggest that their efficacy and safety in practice are largely consistent with the trial data. For many clinicians, and indeed patients, the lack of specific reversal agents has been the main concern with DOAC use since their introduction. Fortunately, this has been addressed for dabigatran with the recent approval of idarucizumab, and the factor Xa inhibitor antidote andexanet alfa could be licensed in the UK later this year. It should also be remembered that even without specific antidotes available, the case fatality rate in patients with major bleeding was lower overall with DOACs than with warfarin.

There are other anticoagulants in development, with the common theme being direct targeting of specific coagulation factors. A factor VIII inhibitor, TB-402, which has a long half-life (approximately three weeks), has been found to be as effective in a one-off dose as 10 days of LMWH in postoperative DVT prophylaxis in a phase 2 trial. Another interesting development is the creation of a factor XI inhibitor (FXI-ASO). It has been observed that patients with congenital mild or moderate deficiency of factor XI often do not have an increased bleeding tendency, but also seem to have a lower risk of VTE. A phase 2 study in 2014 found that FXI-ASO reduced the rate of postoperative DVT compared with LMWH, but without increasing rates of bleeding. Could this be the ‘holy grail’ of anticoagulation, whereby a drug may protect from thrombosis without increasing bleeding risk? Further research is clearly required, and there are many caveats to this treatment, including long duration of anticoagulation (half-life up to three months), injection site reactions and potential cost.

The efficacy of DOACs has yet to be proven in several other indications and clinical scenarios. Dabigatran was less effective than warfarin in patients with mechanical heart valves and it is unknown whether factor Xa inhibitors would be any better. Trials are currently underway in other indications including cancer-associated VTE, peripheral artery disease, coronary artery disease, postcoronary artery stenting in patients with AF, heart failure, antiphospholipid syndrome and VTE prevention in medical patients. It seems likely that over the next few years, DOACs will supersede other anticoagulants as the first-line treatment for many of these indications.

Conclusion
The DOACs are at least as effective, safer and more convenient than VKAs and are revolutionising the approach to prevention and treatment of thromboembolic disease. The decision to anticoagulate, and then which anticoagulant to use, should involve evaluation of several individual patient characteristics including renal function, co-medication, compliance and patient preference. Although regular monitoring is not required, patients on DOAC therapy should still be followed up closely by their clinician to ensure compliance and monitor renal function.

References

Declaration of interests
None to declare.

Dr Wilson is a haematology registrar at Beatson West of Scotland Cancer Centre, Glasgow, Dr Docherty is a cardiology clinical fellow at Golden Jubilee National Hospital, Glasgow, and Dr Gardner is a consultant cardiologist and honorary associate professor for the Scottish National Advanced Heart Failure Service at Golden Jubilee National Hospital, Glasgow.