THROMBO-EMBOLIC VENOUS DISEASE
Non-vitamin K antagonist oral anticoagulants (NOACs) for the management of venous thromboembolism

Andrew D Blann,1 Gregory Y H Lip1,2

INTRODUCTION
Thrombosis is the common pathophysiology responsible for ischaemic heart disease, ischaemic stroke and venous thromboembolism (VTE), and a major contributor to the global disease burden. This effect is markedly more pronounced by considering the view that cancer is also a thrombotic disease. Cardiovascular disease (CVD, manifesting as acute coronary syndromes, myocardial infarction and stroke) is almost entirely related to thrombosis within arteries. However, many of the risk factors for arterial thrombosis are also risk factors for VTE, and in addition VTEs have additional risk factors such as obesity and cancer. Indeed, VTE is a risk factor for subsequent arterial thrombosis. Some risk factors (such as orthopaedic surgery, certain types of valve disease and cardioversion for atrial fibrillation (AF)) are so strong, that anticoagulation is mandatory.

VTE, manifesting principally as deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent complication among hospital inpatients and contributes to longer hospital stays, morbidity and mortality. For example, without antithrombotic prophylaxis, DVT has been documented in over a third of all major orthopaedic operations. Although traditionally considered separate diseases, it is now accepted that DVT and PE are a single clinical entity: 50–80% of those presenting with DVT have evidence of PE while over 80% of those presenting with a PE have asymptomatic DVT. Clinical practice of the prevention and treatment of VTE is compounded by the fact that some risk factors (such as active malignancy) are more likely than others (such as diabetes) to evoke a VTE.

Anticoagulation is considered in numerous diverse clinical situations. However, the variable medical and surgical nature of these situations calls for different drugs for specific indications. For decades, the only options for the treatment and prevention of VTE were a vitamin K antagonist (VKA, principally warfarin), unfractionated heparin, or low molecular weight heparin (LMWH). Although effective, these agents have several disadvantages, such as poor pharmacokinetics and pharmacodynamics (manifesting as variability in absorption and efficacy, and influenced by lifestyle factors such as diet and the use of alcohol), a long half-life (VKAs), and the need for routine blood testing (LMWH excepted). In a clinical setting, the management of these drugs is at best, cumbersome. For example, in seeking to prevent a VTE after surgery, the patient would need to have been started on both warfarin and heparin until the correct dose of the former became evident, which may have taken weeks, at which point the heparin could be discontinued. Long-term management of chronic conditions such as AF called for the patient to have a regular blood test at a frequency of perhaps every 4 weeks.

These and other problems led a decade ago to the development of a new class of drugs, the non-vitamin K antagonist oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants, an alternative term to describe this class of drug being direct-acting oral anticoagulants), which have several advantages over traditional drugs, such as lack of the need for routine blood tests and a reduced frequency of haemorrhage. A major advantage of the NOACs is that they act directly on coagulation factors (thrombin and factor Xa) and so have far more predictable pharmacokinetics. This is in contrast to warfarin, which acts on the liver to reduce the synthesis (and thus plasma levels) of several coagulation factors. The ideal anticoagulant would, in addition to a better safety profile, have minimum interaction with other drugs, high bioavailability, predictable anticoagulant effect to obviate monitoring, and have an antidote. Although neither warfarin nor NOACs have all these features, NOACs are certainly preferable, and antidotes are in development. Key features of anticoagulants are summarised in table 1, their mode of action in figure 1.

At present, four NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) have been approved by the National Institute for Health and Care Excellence (NICE, http://www.nice.org.uk) for the treatment and prevention of VTE. Although these agents are licensed for the prevention of VTE following orthopaedic surgery and AF, this communication aims to provide a brief up-to-date overview of the role of NOACs in the prevention and treatment of VTE.
EPIDEMIOLOGY AND CLINICAL ASPECTS OF VTE

In Western countries the rate of VTE is often cited at ∼100–120 per 100 000 person years, with marked effects of sex, body mass index and age on the risk of developing a thrombus. For example, at age 40–49 years the rate is <100, rising to 150–200 at age 60–69 years and to 450–600 at age 80–89 years. However, VTE overall increases with age, DVT is more common in the young and PE is more common in the old.12–15 Some 40 risk factors for VTE have been identified, and can be classified as genetic, acquired outside hospital, acquired in hospital and environmental, and all can be classified as strong, moderate or weak based on their relative risk (box 1). However, the actual risk of a VTE developing due to any one of these factors is cumulative, although there are no formal guidelines to direct treatment for those at highest risk by virtue of several individual risks. By themselves, Factor V Leiden and obesity bring ORs for risk of VTE of 4.2 and 2.5, respectively. Together, they bring an OR of 7.9.15

Both DVT and PE can initially be difficult to diagnose due to the large number of differential diagnoses. For DVT these include the effects of peripheral artery disease, chronic venous insufficiency, musculoskeletal disease and ruptured...
Box 1 Risk factors for VTE

**Strong risk factors (increased risk >10)**
- Antithrombin deficiency, protein C deficiency, protein S type 1 deficiency
- Active malignancy (with cytotoxic chemotherapy), hip, pelvis or leg fracture, hip or knee replacement, major general surgery (eg, CABG), major trauma, spinal cord injury

**Moderate risk factors (increased risk 2–9)**
- Arthroscopic knee surgery, central venous lines, non-active malignancy congestive heart failure, paralytic stroke, previous VTE, thrombophilia, neurological disease with extremity paresis, superficial vein thrombosis, nphrotic syndrome, atrial fibrillation, obesity (BMI >30)
- Factor V Leiden, fibrinogen G20210A mutation
- Lupus anticoagulant, systemic lupus erythematosus
- Inflammatory bowel disease, HIV, renal transplant recipients
- Pregnancy and puerperium, oral contraceptives, hormone replacement therapy (HRT)
- Low free protein S levels, high factor VIII, high factor IX
- Activated protein C resistance

**Weak risk factors (increased risk <2)**
- Bed rest >3 days, laparoscopic surgery (eg, cholecystectomy), diabetes, smoking, chronic kidney disease, hyperthyroidism, overweight (BMI 25–30), non-blood group O, factor XIII val34Leu mutation, microalbuminuria, prolonged air travel, transient infectious disease.

Pooled from references 8–10

Baker’s cyst, while differential diagnoses for PE include CVD, upper gastrointestinal disease and other forms of pulmonary disease. To aid decision-making, several clinical scoring systems and guidelines have been published.9 16–19 These focus on clinical (immobilisation, history of VTE, tachycardia, risk factors), imaging (duplex ultrasound, ECG, ventilation-perfusion scans) and laboratory (D-dimer, troponins) aspects to determine the probability of an event. Once diagnosed, management of a VTE (as with prevention of a VTE) includes anticoagulation, which has traditionally been VKAs and/or unfractionated heparin or LMWH, but more recently clinical trials have shown that NOACs are at least as or more effective, and have lower rates of haemorrhage.

**Table 2 Renal function and NOACs**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction of absorbed dose that is renally excreted</td>
<td>80%</td>
<td>27%</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>Half-life when CrCl ≥60 mL/min</td>
<td>~14 h</td>
<td>No data</td>
<td>~8.5 h</td>
<td>~8.6 h</td>
</tr>
<tr>
<td>Half-life when CrCl 30–60 mL/min</td>
<td>~18 h</td>
<td>No data</td>
<td>~9 h</td>
<td>~9.4 h</td>
</tr>
<tr>
<td>Half-life when CrCl 15–30 mL/min</td>
<td>~28 h</td>
<td>No data</td>
<td>~9.5 h</td>
<td>~16.9 h</td>
</tr>
<tr>
<td>Not recommended if CrCl &lt;</td>
<td>30 mL/min</td>
<td>15 mL/min</td>
<td>15 mL/min</td>
<td>15 mL/min</td>
</tr>
<tr>
<td>Dosing recommendation when creatinine clearance is falling</td>
<td>CrCl 30–49 mL/min: reduce dose for example, from 150 mg to 110 mg two times per day.</td>
<td>CrCl 15–29 mL/min: reduce dose for example, from 5 mg to 2.5 mg two times per day.</td>
<td>CrCl 15–29 mL/min: reduce dose for example, from 20 mg to 15 mg once a day.</td>
<td>CrCl 15–50 mL/min: reduce dose for example, from 60 mg to 30 mg once a day.</td>
</tr>
</tbody>
</table>

CrCl, creatine clearance; NOAC, non-vitamin K antagonist oral anticoagulant.

CONSIDERATIONS FOR THE CLINICAL USE OF NOACS

These drugs can be classified by their mode of action: dabigatran is a direct thrombin inhibitor while rivaroxaban, apixaban and edoxaban target factor Xa [11] (figure 1). This precision of action brings with it much improved stability and reliability, and thus, a great advantage over warfarin for long-term therapy for VTE.20–29 However, although all NOACs are effective agents, each has subtly different pharmacokinetics and pharmacodynamics, which at the practical level lead to differences in factors such as absorption and half-life. The latter is particularly influenced by renal function, and accordingly creatine clearance must be considered. In the face of falling creatine clearance/glomerular filtration rate, a reduction in the dose is recommended (table 2). Other factors leading to increased plasma levels of NOACs include increasing age (eg, ≥75–80 years) and weight ≤60 kg. Other factors requiring caution with regard to NOAC use include the concomitant use of antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), systemic steroid therapy, history of active gastrointestinal bleeding, recent surgery on a critical organ (the brain, the eye), thrombocytopenia and use of chemotherapy. The practitioner should refer to the summary of product characteristics (SmPC) of each NOAC for specific advice regarding drug interactions.

Polymorphisms in the genes for some of these cytochrome enzymes influence metabolic activity, and therefore plasma levels of substrates (such as NOACs) may be influenced by other medications. Furthermore, dabigatran etexilate (but not dabigatran), rivaroxaban, edoxaban and apixaban are all substrates for P-glycoprotein, a membrane transport molecule whose function is inhibited by drugs such as naproxen, captopril and verapamil. A selected list of interactions are shown in table 3, some of which are so marked as to be contraindicated, whereas in others the dose of the NOAC should be reduced.30 In the face of concomitant dual antiplatelet therapy, advice from a cardiologist should be sought as it is likely an increased risk of bleeding.
Aspirin 81 mg once a day increases risk of bleeding by 12–18%. Dabigatran +32% by 325 mg once a day so not recommended. No effect but increased clinically relevant bleeding: +32% by 325 mg once a day so not recommended. Low dose ≤100 mg once a day used with caution.

DVT, deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.

Table 3  Selected drug interactions with NOACs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>+18%</td>
<td>No data yet.</td>
<td>No effect.</td>
<td>No effect.</td>
</tr>
<tr>
<td>Verapamil</td>
<td>+12–80%*</td>
<td>No data yet.</td>
<td>Minor effect.*</td>
<td>+53%*</td>
</tr>
<tr>
<td>Quinidine</td>
<td>+50%*</td>
<td>No data yet.</td>
<td>+50%*</td>
<td>+77%*</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>No effect.</td>
<td>+40%*</td>
<td>Minor effect.*</td>
<td>No data yet.</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>+12–60%*</td>
<td>No data yet.</td>
<td>Minor effect.*</td>
<td>No effect.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>+70–100%‡</td>
<td>No data yet.</td>
<td>No data yet.</td>
<td>+85%*</td>
</tr>
<tr>
<td>Ketoconazole, itraconazole, voriconazole, posaconazole</td>
<td>+140–150%‡</td>
<td>+100%‡</td>
<td>Up to +160%‡</td>
<td>+90%*</td>
</tr>
<tr>
<td>Clarithromycin, erythromycin</td>
<td>+15–20%*</td>
<td>No data yet.</td>
<td>+30–54%*</td>
<td>+80%*</td>
</tr>
<tr>
<td>Rifampicin, St John’s wort, carbamazepine, phenytoin</td>
<td>−66%‡</td>
<td>−54%‡</td>
<td>Up to −50%</td>
<td>−35%</td>
</tr>
<tr>
<td>Antacids (eg, H2 blockers, proton pump inhibitors)</td>
<td>−12–30%</td>
<td>No data yet.</td>
<td>No effect.</td>
<td>No effect.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No effect.</td>
<td>Increased risk of bleeding of up to 50%.</td>
<td>No effect</td>
<td>No effect.</td>
</tr>
<tr>
<td>Naproxen (as a representative NSAID)</td>
<td>As with caution if creatine clearance 15–50 mL/min.</td>
<td>No data yet.</td>
<td>No data yet.</td>
<td>No data yet.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>81 mg once a day increases risk of bleeding by 12–18%</td>
<td>No effect</td>
<td>No effect</td>
<td>No data yet.</td>
</tr>
<tr>
<td></td>
<td>75 mg once a day</td>
<td></td>
<td></td>
<td>No effect.</td>
</tr>
</tbody>
</table>

Unless stated, data refers to change in area under the curve. Modified from reference 30 and elsewhere, for example, SmPCs.

*Reduce the dose of the NOAC.
†Use with caution if creatine clearance 15–50 mL/min.
‡Use contraindicated/not recommended.

NOAC, non-vitamin K antagonist oral anticoagulant; SmPC, summary of product characteristics.

Table 4  Summary of NOAC trials in VTE

<table>
<thead>
<tr>
<th>Name of trial/reference</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2539</td>
<td>3449</td>
<td>5395</td>
<td>8000</td>
</tr>
<tr>
<td>Frequency of VTE on NOAC versus comparator*</td>
<td>2.4–2.1% (p&lt;0.001 for non-inferiority)</td>
<td>2.1–3.0% (p&lt;0.001 for non-inferiority)</td>
<td>2.3–2.7% (p&lt;0.001 for non-inferiority)</td>
<td>3.2–3.5% (p&lt;0.001 for non-inferiority)</td>
</tr>
<tr>
<td>Principle safety outcome on NOAC versus comparator*</td>
<td>1.6–1.9% (p=0.01 for non-inferiority)</td>
<td>8.1–8.1% (p=0.77 for superiority)</td>
<td>0.6–1.8% (p&lt;0.001 for superiority)</td>
<td>8.5–10.3% (p=0.004 for superiority)</td>
</tr>
<tr>
<td></td>
<td>RE-COVER21</td>
<td>EINSTEIN-DVT23</td>
<td>AMPLIFY26</td>
<td>Hokusai-VTE29</td>
</tr>
</tbody>
</table>

*alternative anticoagulant such as warfarin.

Trials differ markedly in definition of entry criteria, duration, efficacy end point and safety end point.

DVT, deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.
protocols. In contrast, NICE technology appraisals 261 and 287 for rivaroxaban and 341 for apixaban, as well as their respective SmPCs, do not require a parenteral anticoagulant prior to the use of the NOAC, again as per their respective clinical trial protocols. Each NICE technology appraisal and particular SmPC focuses on acute and chronic PE, but fails to refer to unstable PE. Accordingly, each patient must be assessed individually, but it is likely that prophylaxis against PE in an unstable setting would be as in a stable setting. Although there are powerful arguments in favour of the use of these drugs, naturally there may still be a place for the combination of LMWH and warfarin in those for whom an NOAC is inappropriate. Doses for each of the NOACs in the prevention and treatment of VTE are presented in table 3.

### WHICH NOAC TO USE?

The difficulty in determining which particular NOAC has the better benefit/risk ratio for a particular patient lies in the variability of the subjects recruited to the clinical trials and their duration of treatment which, given the multitude of possible confounders (such as renal function), may be impossible to address. For example, the AMPLIFY trial of apixaban included 3% with cancer, whereas 9% of those in the Hokusai trial of edoxaban had cancer.26 29 As cancer is a hypercoagulable disease, the entire patient cohort is at higher risk of a VTE, and therefore more likely to benefit from treatment. Although several commentators have published indirect comparisons between the four NOACs in VTE,36–38 two reported no statistically significant difference in the risk of recurrent VTE or all-cause mortality between the NOACs.37 38

Once it has been established that the patient would benefit from anticoagulation, the choices are warfarin, a LMWH or an NOAC, and factors such as need for heparin/LMWH run-in, patient preference, ability to attend hospital for an international normalised ratio (INR) test, renal function and compliance should be addressed. Ultimately, the clinician would need to fit the NOAC drug to the particular patient profile (see figure 2).

### Switching

Physicians may consider that their patient already on a VKA may benefit from switching to an NOAC. Although no VTE-specific guidance is available, the European Heart Rhythm Association (EHRA) document on NOACs in AF may be useful.30 This guideline recommends that in switching from a VKA to an NOAC, the NOAC can be initiated promptly once the INR is lower than 2.0. If the INR is 2.0–2.5, NOACs can be started immediately or (preferably) the following day. For INR >2.5, the actual INR value and the half-life of the VKA need to be taken into account to estimate the time when the INR value will likely drop to below this threshold value. These are acenocoumarol half-life 8–14 h, warfarin half-life 36–42 h, phenprocoumon half-life 120–200 h. At that time, a new INR measurement can be performed. In switching from a parenteral anticoagulant to NOAC, the latter can be started once the intravenous fractionated heparin (UFH) (half-life around 2 h) is discontinued. However, care is needed in patients with severe renal dysfunction where the elimination of heparin may take longer. NOACs can be initiated when the next dose of LMWH would have been foreseen. The EHRA guideline also offers advice on switching from an NOAC to warfarin, heparin or a LMWH, and in switching to and from antiplatelets, although we again emphasise this is in the setting of AF, not VTE.30

### Haemorrhage

Focusing on the safety profile of NOACs, a pooled analysis of data from 155 537 patients, found that there was no difference in the rate of major bleeding due to rivaroxaban, apixaban or dabigatran when compared with pharmacologically active comparators or VKAs.36 However, two analyses37 38 concluded that apixaban, and then rivaroxaban,
provided the lowest relative risk of major bleeding compared with VKAs, dabigatran and edoxaban (Table 6). Further analyses have reported data on the absolute risk reduction of different forms of haemorrhage, and on the number needed to treat to prevent major bleeding and major bleeding plus clinically relevant non-major bleeding for each NOAC (Table 7).

When faced with any form of haemorrhage, the practitioner must make a clinical decision as to the severity of the bleeding and its likely clinical consequences. This will guide action, which is likely to include determination of recent dosing regimen (time and dose), withholding the NOACs as long as is appropriate and treating symptomatically. Such treatment is likely to include fluid replacement (for maintaining diuresis and blood volume), oxygenation, haemodynamic support and blood transfusion as required. Other potential actions are supporting haemostasis by local compression if feasible (eg, for epistaxis or the tight bandaging of wounds), with endoscopic or surgical intervention to find and treat the source of bleeding, and the correction of abnormal haemostasis with blood products such as factor VII and prothrombin complex concentrate.39 40

**Table 6** Relative risk of haemorrhage between the NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.42 (0.21 to 0.87)</td>
<td>0.37 (0.19 to 0.73)</td>
<td>0.57 (0.29 to 1.15)</td>
</tr>
<tr>
<td>p=0.02</td>
<td>p&lt;0.001</td>
<td>p=0.12</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.74 (0.42 to 1.30)</td>
<td>0.64 (0.38 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>p=0.30</td>
<td>p=0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1.15 (0.66 to 2.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major or clinically relevant non-major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.71 (0.53 to 0.96)</td>
<td>0.54 (0.42 to 0.70)</td>
<td>0.47 (0.37 to 0.61)</td>
</tr>
<tr>
<td>p=0.02</td>
<td>p=0.001</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.50 (1.17 to 1.92)</td>
<td>1.15 (0.95 to 1.39)</td>
<td></td>
</tr>
<tr>
<td>p=0.001</td>
<td>p=0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1.31 (1.02 to 1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data (relative risk and 95% CIs) from reference.36
NOAC, non-vitamin K antagonist oral anticoagulant.

**Antidotes**

Fears of uncontrolled haemorrhage as described above may lead some practitioners to use a VKA (where oral vitamin K is available) instead of an...
NOAC. These fears may be addressed once specific NOAC antidotes become available. A dabigatran antidote (Praxbind (idarucizumab)), a humanised monoclonal antibody fraction is well into clinical development: in the USA the Food and Drug Administration granted accelerated approval for this agent in October 2015. For the factor Xa inhibitors, another experimental antidote, andexanet alfa, has also been submitted for regulatory approval. With a common mode of action, this molecule is likely to be active against each of the factor Xa inhibitors. Andexanet alfa was trialled and found to be an effective antidote against apixaban and rivaroxaban in older healthy participants.

The laboratory

Although an often cited advantage of NOACs is the lack of requirement of routine laboratory monitoring, there are instances where knowledge of the degree of anticoagulation is needed to support clinical action. These include prior to emergency surgery or other invasive procedure, where there is suspicion of overdose, if in acute thrombosis, in renal, liver or heart failure, for proof of compliance, in potential drug-drug interactions, and in trauma, acute medical disease, and malignancy. Should the patient be judged to be overanticoagulated (perhaps on the basis of laboratory data), and so at risk of haemorrhage, prophylactic blood components such as factor VII or prothrombin complex concentrate may be required.

The preferred laboratory methods for assessing the effect of dabigatran are the ecarin clotting time, a chromogenic anti-IIa assay and a dilute thrombin assay, while an antifactor Xa assay (such as the Hep test) is the method of choice for determining the activity of rivaroxaban, apixaban and edoxaban. However, it is unlikely that these tests will be fully available in an emergency setting, and even so may take an unacceptably long time to provide a result. If so in an emergency, although inferior, an activated partial thromboplastin time (APTT) may be used for assessing dabigatran, while a modified or standard prothrombin time may be helpful in determining the effects of a factor Xa inhibitor (table 8).

Guidance from the USA suggest that if APTT is normal, it is unlikely that dabigatran is contributing to bleeding, and if the PT is normal, it is unlikely that rivaroxaban is contributing to bleeding if the last ingestion was within 24 h. However, if APTT is prolonged, it may be assumed that dabigatran is present and that it may be contributing to bleeding, and if PT is prolonged, then it is likely that rivaroxaban is present and that it may be contributing to bleeding.

CONCLUSIONS

NOACs are an exciting new class of drugs that, as a whole, provide at least as good protection from thrombosis as their condition-specific comparator (ie, VKA and/or LMWH), and have better safety profiles. However, there are differences between NOACs in terms of efficacy and safety (eg, rates of major bleeding and/or clinically relevant non-major bleeding (tables 4 and 6)). Accordingly, the practitioner must determine the net clinical benefit of each anticoagulant, and is likely to seek advice from local guidelines, perhaps a product of the local thrombosis committee (figure 2). Therefore, it can be predicted that the increasing visibility of NOACs across a range of conditions (such as AF and after orthopaedic surgery) will provide added confidence in their use in replacing VKAs and LMWHs in the treatment and management of VTE, especially when antidotes become available.

Table 7 Absolute risk reduction for safety outcomes and the number needed to treat to prevent one event for NOACs compared with vitamin K antagonists

<table>
<thead>
<tr>
<th>NOAC</th>
<th>ARR of major bleeding (95% CI)</th>
<th>ARR of major and CRNM bleeding (95% CI)</th>
<th>ARR of fatal bleeding (95% CI)</th>
<th>ARR of intracranial haemorrhage (95% CI)</th>
<th>NNT to prevent one major bleed (95% CI)</th>
<th>NNT to prevent one major and CRNM bleeding (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>0.5 (0.2 to 1.3)</td>
<td>3.2 (1.8 to 4.6)</td>
<td>0.0 (−0.2 to 0.2)</td>
<td>0.2 (−0.1 to 0.5)</td>
<td>183 (80 to infinity)</td>
<td>32 (22 to 57)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.8 (0.3 to 1.5)</td>
<td>0.6 (−0.7 to 1.9)</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.0 (−0.1 to 0.2)</td>
<td>129 (79 to 356)</td>
<td>163 (53 to infinity)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.3 (0.7 to 1.8)</td>
<td>5.4 (4.1 to 6.8)</td>
<td>0.0 (−0.1 to 0.2)</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>80 (55 to 147)</td>
<td>19 (15 to 25)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.2 (−0.3 to 0.8)</td>
<td>1.9 (0.7 to 3.2)</td>
<td>0.2 (0.03 to 0.4)</td>
<td>0.3 (0.1 to 0.5)</td>
<td>415 (132 to infinity)</td>
<td>56 (33 to 189)</td>
</tr>
</tbody>
</table>

Data are ARR (%) and absolute NNT (with 95% CIs). Significant values in bold. From reference. Significance values in bold. From reference.

Table 8 Laboratory monitoring of NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Preferred method(s)</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1. Ecarin clotting time.</td>
<td>Activated partial thromboplastin time (standard or modified).</td>
</tr>
<tr>
<td></td>
<td>2. Dilute thrombin time.</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Antifactor Xa (eg, the Hep test).</td>
<td>Prothrombin time (standard or modified).</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Antifactor Xa (eg, the Hep test).</td>
<td>Dilute prothrombin time.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Little firm data: possibly antifactor Xa.</td>
<td>Little firm data.</td>
</tr>
</tbody>
</table>

NOAC, non-vitamin K antagonist oral anticoagulant.

Table 9 Laboratory monitoring of NOACs

Thrombosis, manifesting as arterial and venous thromboembolism (VTE), and causing major cardiovascular end points, is the leading contributor of mortality and morbidity in the developed world.

The major risk factors for VTE (such as obesity, diabetes, orthopaedic surgery and cancer) are common and well established.

Traditional anticoagulants used to treat and prevent VTEs (vitamin K antagonists and low molecular weight heparin) are effective but have several drawbacks.

Non-vitamin K antagonist oral anticoagulants (NOACs) are a recently developed class of drugs with four major agents: dabigatran, rivaroxaban, apixaban and edoxaban.

NOACs do not need to be routinely monitored with a blood test.

Each of the NOACs has been trialled in the prevention of VTE in atrial fibrillation and after orthopaedic surgery, and in the prevention of recurrent VTE.

A major clinical concern with the use of NOACs is that of renal function. If renal function is poor (creatinine clearance 30–49 ml/min (dabigatran), 15–29 ml/min (apixaban, rivaroxaban) or 15–50 ml/min (edoxaban)) the dose must be reduced, but in severe renal failure (creatinine clearance <30 ml/min (dabigatran) or <15 ml/min (factor Xa inhibitors)), these agents are contraindicated.

In the prevention of recurrent VTEs, NOACs are equally as efficacious as traditional agents, and in many instances have improved safety as measured by a reduced rate of haemorrhage.

There are differences in the rates of various types of haemorrhage brought about by the use of NOACs.

Non-vitamin K antagonist oral anticoagulants and low molecular weight heparin) are effective but have several drawbacks.


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Non-vitamin K antagonist oral anticoagulants (NOACs) for the management of venous thromboembolism

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