Direct oral anticoagulants: integration into clinical practice

Richard P W Cowell

Correspondence to
Dr Richard Cowell,
Department of Cardiology,
Wrexham Maelor Hospital,
Croesnewydd Road, Wrexham,
LL13 7TD, UK;
richard.cowell@wales.nhs.uk

ABSTRACT

The introduction of direct oral anticoagulants (OACs) for the treatment and prevention of thromboembolic disease represents a shift from the traditional vitamin K antagonist-based therapies, which have been the mainstay of treatment for almost 60 years. A challenge for hospital formularies will be to manage the use of direct OACs from hospital to outpatient settings. Three direct OACs—apixaban, dabigatran and rivaroxaban—are widely approved across different indications, with rivaroxaban approved across the widest breadth of indications. A fourth direct OAC, edoxaban, has also completed phase III trials. Implementation of these agents by physicians will require an understanding of the efficacy and safety profile of these drugs, as well as an awareness of renal function, comedication use, patient adherence and compliance. Optimal implementation of direct OACs in the hospital setting will provide improved patient outcomes when compared with traditional anticoagulants and will simplify the treatment and prevention of thromboembolic diseases.

INTRODUCTION

Thromboembolic disease encompasses multiple clinical conditions, including both arterial and venous thromboembolic disorders, and represents a major and growing health burden worldwide.[1][2] Vitamin K antagonists (VKAs) have historically formed the cornerstone of anticoagulant treatment for thromboembolic diseases, especially for long-term treatment, whereas parenteral agents such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux are used for initial, and sometimes longer term, treatment. The use of these anticoagulants is recommended in both the American College of Chest Physicians and the European Society of Cardiology (ESC) guidelines.[3–7] Despite much supporting clinical evidence on the use of these agents, each has major limitations. VKAs are associated with multiple food and drug interactions, as well as wide interindividual variations in pharmacodynamic response, all of which necessitate regular coagulation monitoring and dose adjustments.[8] Initial bridging with faster-acting parenteral anticoagulants may be required, owing to the time taken to reach therapeutic effect (eg, 36–72 h with warfarin). Parenteral anticoagulants (UFH, LMWH and fondaparinux) are less convenient compared with oral medications.[9] These limitations may contribute to suboptimal adherence to long-term treatment regimens.

The development and introduction of direct oral anticoagulants (OACs) for the treatment and prevention of thromboembolic disorders represents a major shift from the traditional VKA-based therapies. Four direct OACs—apixaban, dabigatran, edoxaban and rivaroxaban—have completed large phase III clinical studies for different thromboembolic conditions. These direct OACs bind directly to key proteins of the clotting cascade, leading to the inhibition of fibrin formation (figure 1). In addition to their oral administration, the direct OACs have the advantage of predictable pharmacokinetic and pharmacodynamic properties, few drug and food interactions, and a rapid onset (maximum effect within 4 h) and offset (half-lives <24 h) of action.[10]

These direct OACs provide an alternative to traditional VKA-based therapies for the treatment and prevention of thromboembolic disease, but physicians tend to have less clinical experience with these agents and are less familiar with their key properties. A challenge for hospital formularies is to integrate use of these new agents appropriately across a broad range of thromboembolic diseases and to understand their use in both hospital and outpatient settings. Physicians and formulary committees need to understand the efficacy and safety profiles of these drugs in the treatment of thromboembolic disease. Knowledge of dosing regimens, administration method, management of switching and reversal, and handling adverse events (AEs) are also essential for the proper implementation of these direct OACs.

This article reviews the results of the key phase III trials of the direct OACs in the thromboembolic indications in which they are approved and explores the clinical challenges and administrative considerations in managing the use of these agents in the hospital and outpatient settings. These considerations include dose administration and adjustments, the use of comedications, measuring anticoagulant activity and switching to and from other anticoagulants.

Licensed indications

Apixaban, dabigatran and rivaroxaban have been approved in various thromboembolic indications (table 1), and edoxaban is likely to be approved in some indications in the EU in the near future. Rivaroxaban is the first of the agents to receive European approval for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) and elevated cardiac biomarkers,[11] but to date there has been comparatively little use of rivaroxaban in this indication in routine clinical practice and the data are not discussed further. Rivaroxaban and apixaban have also completed phase III studies for venous thromboembolism (VTE) prevention in acute medical patients,[12][13] and dabigatran has been studied in patients with atrial fibrillation (AF) and mechanical heart valves,[14] but these agents are not approved in these indications.

Figure 1 Key targets of the direct oral anticoagulants in the coagulation cascade.
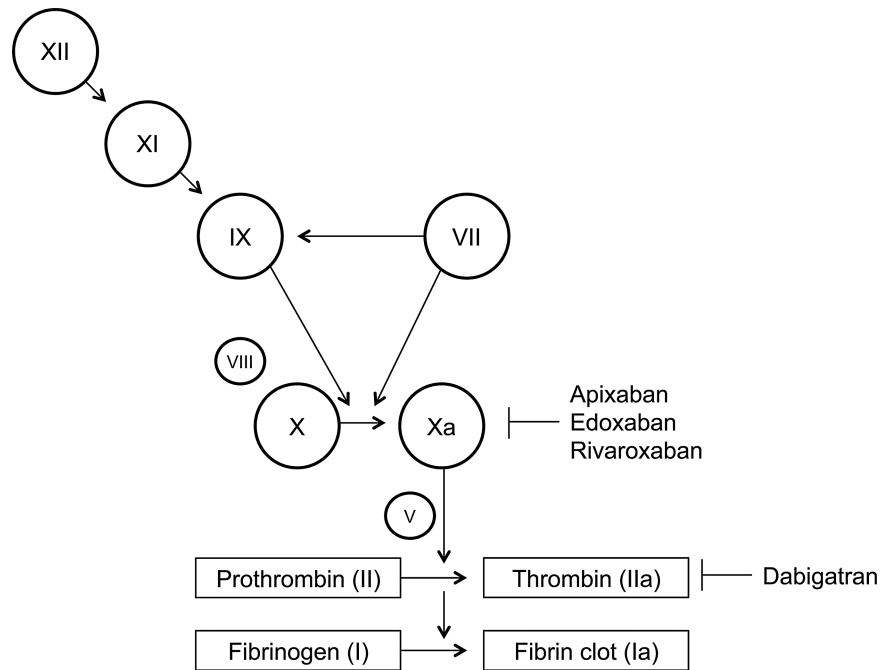
CLINICAL TRIAL DATA IN LICENSED INDICATIONS
Prevention of venous thromboembolism after elective hip or knee replacement in adults

Patients are at high risk of VTE after major elective orthopaedic surgery. Without thromboprophylaxis, the estimated incidence of deep vein thrombosis (DVT) is 40–60%.[15] Apixaban, dabigatran and rivaroxaban are all approved in the EU for the prevention of VTE after elective hip or knee replacement surgery. The approvals are based on the results of phase III trials in which each drug was compared with standard thromboprophylaxis with subcutaneous enoxaparin. Edoxaban has not undergone a European phase III study in this indication.

The ADVANCE trials compared apixaban (started 12–24 h after surgery) with enoxaparin 30 mg twice daily started 12–24 h after surgery (used in North America; ADVANCE-1)[16] or 40 mg once daily started 12 h before surgery (used in Europe) after elective total hip (THR; ADVANCE-3) or total knee (TKR; ADVANCE-2) replacement surgery in a total of 11 659 patients.[17 18] Apixaban was shown to be superior to enoxaparin 40 mg once daily for the reduction of the incidence of VTE (reduction in occurrences: 64% THR; 38% TKR), with no significant differences in the incidence of major bleeding

events.[17 18] However, apixaban did not meet non-inferiority criteria compared with enoxaparin 30 mg twice daily.[16]

Dabigatran has also obtained mixed results from phase III trials for the prevention of VTE after THR (RE-NOVATE I[19] and II[20]) and TKR (RE-MODEL[21] and RE-MOBILIZE[22]), which involved 10 265 patients. Dabigatran, at both doses tested (150 mg once daily and 220 mg once daily, starting with a half-dose 1–4 h postsurgery), was non-inferior to enoxaparin 40 mg once daily (started the evening before surgery), with no statistical difference in the incidence of major bleeding;[19–21] however, dabigatran (starting with a half-dose 6–12 h postsurgery) failed to meet non-inferiority criteria against enoxaparin 30 mg twice daily, started 12–24 h after surgery.[22]

Rivaroxaban has been studied in four prospective phase III studies: RECORD1 and RECORD2 involved patients undergoing THR surgery, and RECORD3 and RECORD4 involved patients undergoing TKR surgery.[23–26] Unlike apixaban and dabigatran, rivaroxaban (started 6–8 h after surgery) demonstrated superior efficacy for the prevention of total VTE versus all enoxaparin regimens (40 mg once daily started 12 h before surgery, RECORD1–3; 30 mg twice daily started 12–24 h after surgery, RECORD4), with no significant differences in major

Table 1 Summary of the major licensing of direct oral anticoagulants by indication

Drug name	VTE prevention after elective hip or knee replacement surgery	Stroke prevention in non-valvular AF	Acute VTE treatment and secondary prevention		Secondary prevention of atherothrombotic events after ACS
			DVT	PE	
Apixaban	EMA and FDA	EMA and FDA	–	–	–
Dabigatran	EMA	EMA and FDA	FDA	FDA	–
Rivaroxaban	EMA and FDA	EMA and FDA	EMA and FDA	EMA and FDA	EMA*
Edoxaban	Not currently approved	Not currently approved	Not currently approved	Not currently approved	Not currently approved

*Rivaroxaban (2.5 mg twice daily) is approved by the EMA for the secondary prevention of atherothrombotic events after ACS in combination with standard antiplatelet therapy (acetylsalicylic acid with or without clopidogrel or ticlopidine) in adult patients with elevated cardiac biomarkers.
ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; EMA, European Medicines Agency; FDA, Food and Drug Administration; PE, pulmonary embolism; VTE, venous thromboembolism.

bleeding events. A pooled analysis of all four studies, involving 12 729 patients, demonstrated a 50% reduction (p=0.001) in the composite of symptomatic VTE and all-cause mortality with rivaroxaban compared with enoxaparin.[27] The incidence of bleeding was similar (6.6% vs 6.2%) during active treatment. Rivaroxaban has also been studied in a phase IV, non-interventional open-label study (XAMOS), in which the attending physician determined which type and regimen of drug was used. This study further confirmed the favourable benefit–risk profile of rivaroxaban in routine clinical practice.[28]

Overall, these results are somewhat mixed, which may partly be explained by variations in the dosing approach of the direct OAC and comparator regimen arms. However, all three direct OACs were either non-inferior or superior to the European enoxaparin regimen (40 mg once daily). In contrast to standard practice with enoxaparin in Europe, administration of direct OACs is started after surgical wound closure.

Venous thromboembolism: treatment and secondary prevention

VTE (DVT and pulmonary embolism (PE)) is associated with significant morbidity and mortality, and its incidence increases with age.[29] Rivaroxaban has been approved in the EU and the USA for the treatment of DVT and PE and for the prevention of recurrent VTE. Apixaban, dabigatran and edoxaban have also completed phase III trials for both acute and secondary prevention of VTE (table 2); they are not yet licensed in this indication in the EU, but dabigatran has recently been approved for VTE treatment in the USA.

It is important to note the different approaches of the phase III studies of direct OACs for VTE treatment. For acute treatment, rivaroxaban[30 31] and apixaban,[32] given as single-drug treatments, were compared with standard parenteral anticoagulation overlapping with and transitioning to a VKA; in contrast, dabigatran[33] and edoxaban[34] were compared with standard therapy after induction by a parenteral agent. Only rivaroxaban was tested in separate studies in patients with DVT (without PE) or PE (with or without DVT).[30 31] All four direct OACs were non-inferior to standard therapy for prevention of recurrent VTE. Compared with standard therapy, apixaban (in AMPLIFY)[32] and rivaroxaban (in EINSTEIN PE)[31] led to significantly less major bleeding, whereas rivaroxaban (in EINSTEIN DVT),[30] dabigatran (in RE-COVER and RE-COVER II)[33 35] and edoxaban (in Hokusai-VTE)[34] led to significant reductions in clinically relevant bleeding. Pooled analyses of the EINSTEIN DVT and EINSTEIN PE studies, and the RE-COVER studies, have supported the overall efficacy and safety of rivaroxaban and dabigatran, including in high-risk subgroups such as the elderly, patients with low body weight and those with unprovoked initial VTE.[35 36]

Because it is not standard practice to give long-term anticoagulation for the prevention of recurrent VTE, in the extended treatment studies, apixaban (AMPLIFY-EXT), rivaroxaban (EINSTEIN EXT) and dabigatran (RE-SONATE) were all compared with placebo.[30 37 38] All three direct OACs were associated with significant reductions in the incidence of recurrent VTE with a low incidence of major bleeding (table 2).[30 37 38] However, long-term or even lifelong anticoagulation is recommended for some patients who have suffered a VTE.[6] Uniquely, dabigatran was directly compared with warfarin for long-term secondary prevention of VTE and was shown to have non-inferior efficacy, with 50% fewer major bleeding events but a significant increase in the incidence of ACS (0.9% vs 0.2%; p=0.02).[38]

Stroke prevention in atrial fibrillation

More than six million people suffer from AF in the EU,[3] and the prevalence of AF increases with age.[39] Patients with AF have an increased risk of stroke, and stroke-associated deaths in the EU total more than one million annually.[40] VKAs such as warfarin have proved remarkably effective in reducing this risk of stroke. Despite this, patients with AF at high risk of stroke are often undertreated,[41] and VKAs are associated with limitations. In the EU, rivaroxaban, apixaban and dabigatran are approved for stroke prevention in patients with non-valvular AF.

The phase III trials for apixaban (ARISTOTLE),[42] dabigatran (RE-LY),[43] rivaroxaban (ROCKET AF)[44] and edoxaban (ENGAGE-AF)[45] involved large numbers of patients with non-valvular AF (between ~14 000 and 18 000) and evaluated the agents' efficacy in the prevention of stroke or systemic embolism compared with that of dose-adjusted warfarin (target international normalised ratio (INR) 2.0–3.0). In the EU, apixaban and rivaroxaban were approved at the doses tested. Dabigatran is approved at the 150 mg twice-daily dose, with 110 mg twice daily approved for at-risk groups in whom dose adjustment may be required.[46] These groups include patients aged ≥80 years and those taking concomitant verapamil, but dose reduction can also be considered, based on assessment of thromboembolic and bleeding risk, for individuals aged 75–80 years, those with moderate renal impairment, patients with gastritis, oesophagitis or gastroesophageal reflux, and any other patients at increased risk of bleeding.[46]

In these phase III trials, dabigatran 150 mg twice daily and apixaban 5 mg twice daily demonstrated superiority to warfarin in the reduction of stroke and systemic embolism (34% risk reduction for dabigatran;[43] 21% risk reduction for apixaban;[42] p<0.001 for both). Edoxaban 60 mg once daily was superior (p=0.02) to warfarin, whereas edoxaban 30 mg once daily was non-inferior (p<0.005 for non-inferiority) to warfarin.[45] Dabigatran 110 mg twice daily and rivaroxaban 20 mg once daily were non-inferior to warfarin (p<0.001 for non-inferiority).[43 44] In subsequent subgroup analyses, the relative safety and efficacy of these agents was similar regardless of patients' history of stroke or transient ischaemic attack.[47–49] Dabigatran (150 mg twice daily) is the only agent to have achieved significant reductions in both ischaemic stroke (p=0.03) and haemorrhagic stroke (p<0.001), whereas apixaban, for example, reduced the rate of haemorrhagic stroke only.[42]

A concern with anticoagulants is the increased risk of bleeding at critical sites or bleeding that proves fatal. Rivaroxaban and dabigatran (150 mg twice daily) resulted in similar incidences of major bleeding compared with warfarin (p=0.58 and p=0.31, respectively), whereas apixaban reduced the risk of major bleeding by 31% (p<0.001); however, the definitions of 'major bleeding' varied by trial. The 150 mg twice-daily dose of dabigatran was associated with a 19% reduction of life-threatening haemorrhage (p=0.04), and rivaroxaban reduced the risk of intracranial (0.5%/year vs 0.7%/year, respectively; p=0.02), fatal (0.2%/year vs 0.5%/year, respectively; p=0.003) and critical (0.8%/year vs 1.2%/year, respectively; p=0.007) bleeding compared with dose-adjusted warfarin. Rivaroxaban and dabigatran were associated with more gastrointestinal bleeding events compared with warfarin in patients with AF, and the dabigatran 150 mg dose led to a slight but significant increase in the rate of myocardial infarction.[43]

In the absence of true direct (head-to-head) clinical trials, comparisons of results across different trials remain inadvisable due to different study populations and trial designs. For example, RE-LY included patients at lower risk of stroke than the other studies.[43] ROCKET AF included a higher-risk

Table 2 A summary of the study design and key findings from direct oral anticoagulant phase III trials in the acute and long-term treatment of venous thromboembolism

Drug	Trial (number of patients)	Indication	Dose and duration	Comparator	Recurrent VTE or VTE-related death		Major bleeding	
					Study drug events/total (%)	Comparator events/total (%)	Study drug events/total (%)	Comparator events/total (%)
Apixaban	AMPLIFY[32] (n=5395)	Acute VTE treatment	10 mg twice daily for 7 days, then 5 mg twice daily for 6 months	Enoxaparin→VKA	59/2691 (2.3)	71/2704 (2.7)	15/2676 (0.6)	49/2689 (1.8)
	AMPLIFY-EXT[37] (n=2486)	Secondary prevention of VTE	2.5 mg twice daily or 5 mg twice daily for 12 months	Placebo	2.5 mg: 32/840 (3.8); 5 mg: 34/813 (4.2)*	96/829 (11.6)*	2.5 mg: 2/840 (0.2); 5 mg: 1/813 (0.1)	4/829 (0.5)
Dabigatran	RE-COVER[33] (n=2539)	Acute VTE treatment	6 months' 150 mg twice daily after initial parenteral anticoagulation for ≥5 days	VKA	30/1274 (2.4)†	27/1265 (2.1)	20/1274 (1.6)	24/1265 (1.9)
	RE-COVER II[35] (n=2589)	Acute VTE treatment	6 months' 150 mg twice daily after initial 5–11 days' parenteral anticoagulant	VKA	30/1279 (2.3)†	28/1289 (2.2)	15/1279 (1.2)	22/1289 (1.7)
	RE-MEDY[38] (n=2856)	Secondary prevention of VTE	150 mg twice daily for 6–36 months	VKA	26/1430 (1.8)†	18/1426 (1.3)	13/1430 (0.9)	25/1426 (1.8)
	RE-SONATE[38] (n=1343)	Secondary prevention of VTE	150 mg twice daily for 6 months	Placebo	3/681 (0.4)‡	37/662 (5.6)‡	2/681 (0.39)	0/662 (0)
Rivaroxaban	EINSTEIN DVT[30] (n=3449)	Acute DVT	15 mg twice daily for 21 days, then 20 mg once daily for 3, 6 or 12 months	Enoxaparin→VKA	36/1731 (2.1)†	51/1718 (3.0)	14/1718 (0.8)	20/1711 (1.2)
	EINSTEIN PE[31] (n=4832)	Acute PE (with or without DVT)	15 mg twice daily for 21 days, then 20 mg once daily for 3, 6 or 12 months	Enoxaparin→VKA	50/2419 (2.1)†	44/2413 (1.8)	26/2412 (1.1)	52/2405 (2.2)
	EINSTEIN EXT[30] (n=1196)	Secondary prevention of VTE	20 mg once daily for 6 or 12 months	Placebo	8/602 (1.3)§	42/594 (7.1)	4/598 (0.7)	0/590 (0.0)
Edoxaban	Hokusai-VTE[34] (n=8240)	Acute VTE	3, 6 or 12 months of edoxaban 60 mg¶ once daily after a minimum 5 days' heparin	Heparin→ warfarin	130/4118 (3.2)†	146/4122 (3.5)	56/4118 (1.4)	66/4122 (1.6)

*Includes death from any cause.
†Statistically significant non-inferiority demonstrated to comparator.
‡Includes death from any cause.
§Statistically significant superiority demonstrated over comparator.
¶30 mg once daily in patients with creatinine clearance 30–50 mL/min, body weight ≤60 kg or receiving concomitant treatment with strong P-glycoprotein inhibitors.
DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

population with a mean CHADS$_2$ score of 3.5[44] compared with 2.1 in both RE-LY[43] and ARISTOTLE[42]; in ENGAGE-AF, 77% of patients had a CHADS$_2$ score ≤3.[45]

Apixaban has also been evaluated in a smaller trial (AVERROES), in which patients for whom VKA therapy was not suitable were assigned to receive either apixaban or acetylsalicylic acid (ASA).[50] Apixaban reduced the risk of stroke by >50% (p<0.001) compared with ASA, without significantly increasing the risk of major bleeding or intracranial haemorrhage.[50] ASA is no longer recommended for the prevention of stroke, given that the results of numerous trials have demonstrated its low efficacy in stroke prevention compared with warfarin and its increased bleeding risk compared with placebo.[51 52] However, there is still a perception among physicians that it can be used. The termination of the AVERROES trial, owing to the treatment benefit of apixaban, supports the improved benefit–risk profile of direct OACs over ASA for this indication.[50]

PRACTICAL ASPECTS OF ORAL ANTICOAGULANT THERAPY
Vitamin K antagonist control
Management of the INR can be problematic. The ESC suggests a time in therapeutic range (TTR) for the INR (usually 2.0–3.0) of 70% as the minimum threshold that constitutes good management of patients with AF.[51] Data from real-life practice suggest that this level of control is not achieved in many patients.[53] Two possible reasons for suboptimal TTR are poor patient adherence and/or the patient's INR being affected by concomitant medications, drug–food interactions or genetic polymorphisms. Patients who fall into these categories therefore represent groups that could benefit from fixed-dose therapy with the direct OACs.

In trials of the direct OACs for the prevention of AF-related stroke and for the treatment and secondary prevention of VTE, patients receiving warfarin had a mean TTR between 55% (ROCKET AF[44]) and 65% (RE-MEDY[38]). In subanalyses of the RE-LY and ARISTOLE trials in patients with AF, it was found that the overall profiles of dabigatran and apixaban were consistent against warfarin regardless of TTR.[54 55] However, the composite outcome of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death and major bleeding favoured dabigatran when the TTR was ≤57%, but above this level, the composite outcome was not significantly different between dabigatran and warfarin.[54] Similarly, the composite of stroke/SE, all-cause death and major bleeding favoured apixaban for TTR<60.5%, but for higher TTRs, apixaban was not significantly different from warfarin.[55] These data may provide a guidance TTR threshold below which patients receiving VKA could be switched to dabigatran or apixaban.

Pharmacokinetics of direct oral anticoagulants
The pharmacokinetic profiles of direct OACs influence dose and regimen. Peak plasma concentrations of the direct OACs are reached within 4 h of oral administration, which is considerably quicker than among the VKA-based therapies. The half-lives of the direct OACs range from 5 to 15 h[11 56 57]; however, in renally impaired patients, slower elimination can affect drug exposure. Approximately one-third of an orally absorbed rivaroxaban dose is eliminated unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and the faeces.[11] Apixaban has multiple elimination pathways, with approximately 27% of total clearance via renal excretion.[58] Dabigatran is administered as an oral prodrug that

is converted into its active form in the liver; the majority (85%) of the unchanged drug is excreted by the kidneys.[46]

Bleeding risk with direct oral anticoagulants
All anticoagulants are associated with an increased risk of bleeding. There have been a number of case studies showing serious bleeding events associated with dabigatran use.[59 60] However, in phase III studies, 30-day mortality after the first major bleeding event tended to be lower with dabigatran (9.1%) than with warfarin (13.0%; p=0.057).[61] In an investigation of postmarketing reports, the risk of bleeding was found to be consistent to that reported in RE-LY, when dabigatran was used according to recommendations.[62] This highlights the importance of adhering to the recommended dose. However, bleeding may still cause anxiety to patients and be of concern to physicians. It is important to minimise the risk by advocating the proper use of anticoagulants within the hospital setting and understanding procedures for the optimal management of bleeding. Additionally, there is a need to consider the dosing of these drugs in certain patient populations, strategies for switching between anticoagulants and how to deal with emergency situations.

Administration and drug adherence
Ease of administration influences patient adherence and outcomes, and an advantage of direct OACs is that they are administered orally. This could help to reduce the length of hospitalisation, for example, when patients are treated for VTE and have no need for initial subcutaneous heparin injections. In a subanalysis of the EINSTEIN PE and EINSTEIN DVT trials, hospitalised patients who received initial treatment with rivaroxaban for DVT or PE had a significantly shorter length of stay compared with patients who received enoxaparin/VKA across regions and countries (p<0.0001 for both groups).[63] Rivaroxaban can also be administered as a crushed tablet and given mixed with food or via a nasogastric tube in patients who struggle to swallow whole tablets[64]; however, no similar studies have been performed for apixaban administration, and dabigatran capsules should not be crushed or chewed before swallowing.[46]

For long-term use, rivaroxaban is given once daily (for AF and long-term VTE treatment),[11] whereas other direct OACs are given twice daily (table 3). Edoxaban, if approved, would also be given once daily in this indication. For many cardiovascular diseases, once-daily medication administration has been shown to be more convenient for patients, resulting in improved patient compliance and persistence.[65] Once-daily dosing may confer further advantages in terms of outpatient management, patient outcomes and pharmacy management.[66] However, the impact of a missed dose on pharmacological effect may be greater than for a drug dosed more frequently.[67] Product packaging can also play a role in patient compliance. Dabigatran etexilate must be stored in airtight bottles to protect it from moisture and maintain its pH; this is a requirement for sufficient adsorption. Dabigatran administration may therefore be an issue for some elderly patients in whom compliance is improved by the use of dispensers, in which the other direct OACs can be stored.[68]

Duration of treatment
Postsurgical VTE prophylaxis requires only short-term anticoagulation, whereas patients with AF will often receive lifelong anticoagulant treatment. For VTE treatment, however, the duration of anticoagulation must be considered carefully. The

Table 3 Dose regimens and adjustments required in certain patient populations, by agent and indication, for direct oral anticoagulants currently approved in Europe[11 46 58]

| Drug and indication | Normal dose | Renal function (CrCl, mL/min) | | | | Elderly patients | Hepatic impairment |
		51–80*	30–50†	15–29	<15		Liver enzymes >2 ULN
Apixaban							
VTE prophylaxis	2.5 mg twice daily	2.5 mg twice daily	2.5 mg twice daily	Use with caution	Not recommended	No adjustment	With caution‡
AF	5 mg twice daily	5 mg twice daily§	5 mg twice daily§	2.5 mg twice daily	Not recommended	2.5 mg twice daily§	With caution‡
Dabigatran							
VTE prophylaxis	220 mg once daily	220 mg once daily	150 mg once daily	Contraindicated	Contraindicated	(>75 years) 150 mg once daily	Not recommended
AF	150 mg twice daily	150 mg twice daily	150 mg twice daily¶	Contraindicated	Contraindicated	(≥80 years) 110 mg twice daily**	Not recommended
Rivaroxaban							
VTE prophylaxis	10 mg once daily	10 mg once daily	10 mg once daily	Use with caution	Not recommended	No adjustment	††
AF	20 mg once daily	20 mg once daily	15 mg once daily	15 mg once daily	Not recommended	No adjustment	††
VTE, acute treatment	15 mg twice daily for 21 days, then 20 mg once daily	15 mg twice daily for 3 weeks, then 20 mg once daily	15 mg twice daily for 3 weeks, then 20 mg once daily‡‡	15 mg twice daily for 3 weeks, then 20 mg once daily‡‡	Not recommended	No adjustment	††
VTE, extended treatment	20 mg once daily	20 mg once daily	20 mg once daily‡‡	20 mg once daily‡‡	Not recommended	No adjustment	††

*CrCl 50–80 mL/min for dabigatran and rivaroxaban.
†CrCl 30–49 mL/min for rivaroxaban.
‡Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk and not recommended in patients with severe hepatic impairment.
§With at least two of the following characteristics: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.
¶In patients at high risk of bleeding, a dose reduction of dabigatran to 110 mg twice daily should be considered.
**Patients aged 75–80 years may take 110 mg twice-daily dose at the discretion of the physician.
††Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child–Pugh B and C.
‡‡A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk of recurrence of DVT or PE.
AF, atrial fibrillation; CrCl, creatinine clearance; ULN, upper limit of normal; VTE, venous thromboembolism.

Table 4 Recommendations for use of concomitant medications with the direct oral anticoagulants[11 46 58]

Concomitant medication	Mechanism	Direct oral anticoagulant		
		Apixaban	Dabigatran	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition		No clinically relevant interaction	No clinically relevant interaction
Digoxin	P-gp competition	No clinically relevant interaction	No clinically relevant interaction	No clinically relevant interaction
Verapamil	P-gp competition (and weak CYP3A4 inhibition)		Use with caution	
Quinidine	P-gp competition		Use with caution	
Amiodarone	P-gp competition		Use with caution	
Dronedarone	P-gp competition and CYP3A4 inhibition		Contraindicated	Avoid use
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	Not recommended	Contraindicated	Not recommended
Fluconazole	Moderate CYP3A4 inhibition			No clinically relevant interaction
Cyclosporin	P-gp competition		Contraindicated	
Clarithromycin	P-gp competition and CYP3A4 inhibition		Use with caution	No clinically relevant interaction, but use with caution in patients with renal impairment
HIV protease inhibitors (eg, ritonavir)	P-gp and BCRP competition or induction; CYP3A4 inhibition	Not recommended		Not recommended
Rifampicin; St. John's wort; carbamazepine; phenytoin	P-gp/BRCP and CYP3A4/CYP2J2 induction	Use with caution	Avoid use	Use with caution

Dark grey, contraindicated/not recommended/avoid use; light grey, use with caution; empty, no information available.
BRCP, breast cancer resistance protein; CYP, cytochrome P450; P-gp, P-glycoprotein.

length of VTE therapy was 3, 6 or 12 months in the EINSTEIN trials,[30 31] 6 months in AMPLIFY[32] and the RE-COVER studies,[33 35] and 3–12 months in Hokusai-VTE.[34] Data from a study of patients receiving OAC therapy after a second VTE suggest that indefinite treatment resulted in a lower rate of recurrence than treatment for 6 months; however, a higher risk of bleeding was also noted with extended treatment.[69] The duration of therapy should therefore be individualised after assessment of the benefit–risk profile. Three months of anticoagulant treatment is recommended for acute VTE associated with reversible risk factors or in cases of unprovoked VTE in which bleeding risk is high. In cases of unprovoked VTE with low or moderate bleeding risk, or in patients suffering from active cancer (in which the risk of VTE recurrence is threefold higher[70]), extended therapy is recommended.[6]

General contraindications and dose adjustments with direct oral anticoagulants

There are limited data on the use of direct OACs in some patient populations. Currently, none of the direct OACs are approved for use in paediatric populations, pregnant individuals or those who are breastfeeding.[11 46 58] For patients with cancer, the guidelines prefer LMWH.[6] The maintenance of sufficient anticoagulation by dose adjustment can be a challenge in some groups. For most cases in which direct OACs are administered, no dose adjustment is required. In certain cases—for example, in patients who have renal or hepatic insufficiency, elderly patients or those at higher risk of bleeding—dose adjustments are recommended (table 3).

Apixaban and rivaroxaban are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.[11 58] Apixaban treatment is contraindicated in cases of severe hepatic impairment (eg, Child–Pugh class C), whereas cirrhotic patients with Child–Pugh class B or C should not be treated with rivaroxaban. A study of apixaban

in healthy subjects or those with mild or moderate hepatic impairment (Child–Pugh class A and B) demonstrated similar anti-Factor Xa activity and INR between the groups. Consequently, dose adjustment of apixaban is not necessary, but it should be used with caution in cases of mild-to-moderate hepatic impairment. Patients with liver disease were excluded from clinical trials of dabigatran; consequently, dabigatran use is contraindicated in cases in which hepatic impairment or liver disease is expected to have any impact on survival.[46]

Given that apixaban, dabigatran and rivaroxaban are all associated with some degree of renal clearance, impaired renal function can result in increased plasma concentrations. For long-term drug therapy, particularly in elderly patients (because renal function declines with age), renal function and detection of chronic kidney disease should be determined before therapy is initiated. Additionally, recent practical guidelines on the use of new OACs in patients with non-valvular AF recommend 6-monthly monitoring of renal function in patients who have creatinine clearance (CrCl) 30–60 mL/min, are >75 years old or are fragile, and at 3-monthly intervals if the CrCl is in the range 15–30 mL/min.[71] Clinical studies of the direct OACs usually define renal function in terms of CrCl (in mL/min). It is important to determine renal function using the Cockcroft–Gault formula,[72] which provides a more accurate estimate of renal function compared with measuring plasma creatinine alone or relying on the estimated glomerular filtration rate reported by the laboratory, especially in patients with extreme weight and age characteristics (see equation below).

$$\text{Cockcroft} - \text{Gault equation} = [(140 - \text{age[years]}) \times \text{weight[kg]}(\times 0.85 \text{ if female})] / (72 \times \text{serum creatinine[mg/dL]})$$

In clinical trials of direct OACs in stroke prevention, VTE and orthopaedic surgery, patients with CrCl <30 mL/min were

generally excluded. Patients with CrCl <25 mL/min were excluded from ARISTOTLE. The direct OACs are not recommended for patients with CrCl <15 mL/min; for patients with severe renal insufficiency (CrCl 15–29 mL/min), risk assessments by the physician are necessary. Dabigatran is not recommended in patients with severe renal insufficiency and apixaban is to be used with caution in these patients, whereas certain dose adjustments are required for rivaroxaban use in AF but not in VTE treatment (unless the patient's risk of bleeding is considered to outweigh the risk of recurrence; table 3).[11 46 58]

Comedication use with direct oral anticoagulants

Patients requiring anticoagulant treatment often receive comedications to treat comorbidities, and patient exposure to direct OACs can be influenced by drugs that interfere with their metabolism. It is important for physicians to be mindful of any interactions that may alter plasma concentrations of direct OACs; however, several widely used drugs have been demonstrated to have no interaction with these agents (table 4).

Apixaban and rivaroxaban are all substrates for cytochrome P450 (CYP) isoforms, such as CYP3A4, and for the cell efflux transporter P-glycoprotein (P-gp). Apixaban and rivaroxaban plasma concentrations have been shown to increase to a clinically relevant degree in the presence of ketoconazole and ritonavir, which are strong inhibitors of CYP3A4 and P-gp. In view of the associated increased risk of bleeding, concomitant treatment with systemic azole antimycotics or HIV protease inhibitors is not recommended. For apixaban or rivaroxaban, the concomitant use of less potent inhibitors of CYP3A4 and/or P-gp results in smaller increases in plasma concentrations that are not considered clinically relevant.[11 58] CYP3A4 inducers should be administered with caution. Edoxaban elimination is only slightly dependent on CYP3A4 mechanisms and is mostly mediated by P-gp.[73]

Dabigatran is not metabolised by CYP enzymes but is dependent on P-gp transporters. Consequently, strong P-gp inhibitors are expected to increase dabigatran plasma concentrations,[46] and dose adjustments and caution are therefore required for dabigatran with the use of P-gp inhibitors and inducers. Particular care is also needed in patients with renal impairment who are taking comedications, owing to the high dependence of dabigatran on renal elimination and consequent possible increases in exposure.[11 46 58]

Caution is needed in the treatment of patients in whom direct OACs are administered concomitantly with antiplatelet regimens or non-steroidal anti-inflammatory drugs (NSAIDs), owing to these agents' influence on haemostasis and increased bleeding risk. Coadministration of these agents was allowed within certain limits in some studies. Data from the RECORD and EINSTEIN programmes found that concomitant use of NSAIDs resulted in an increase in bleeding events with both rivaroxaban and enoxaparin.[74 75]

Measuring anticoagulation activity and managing bleeding

Conventional anticoagulants require frequent clinic visits and subsequent dose adjustments to monitor and control anticoagulation intensity.[8] Owing to their wide therapeutic window and predictable pharmacokinetic profile, such monitoring is not usually required with direct OACs,[8] and this can alleviate the excessive burden that regular clinic appointments can represent. However, this frequent monitoring can provide reassurance to both patient and physician and is therefore not always considered to be an inconvenience. Without the need to attend warfarin clinics, regular reviews should be considered to provide a means to reassure patients and to ensure that physicians are able

to follow their clinical progress. This is particularly important in patients with comorbidities or those undergoing neuraxial anaesthesia (in which there is an increased risk of developing haematoma) and is already a recommendation in patients with renal insufficiency.[72]

In hospitals that are equipped with appropriate facilities, laboratory measurement of direct OAC plasma concentration may be appropriate in certain situations. Examples include confirmation of compliance, suspected overdose, cases of life-threatening bleeding or cases in which imminent surgery is required. Clinically relevant drug–drug interactions can also alter bleeding risk and should be taken into account; however, known drug–drug interactions are rare for these agents.

Although there are no well-established methods of measuring the anticoagulant activity of direct OACs (the INR is not a valid measure), alternative options have been studied. As a result of the direct linear relationship of anti-Factor Xa activity with apixaban plasma concentration, the Rotachrom Heparin chromogenic assay has been suggested for the indirect measurement of apixaban levels.[58] Rivaroxaban has been measured over a wide range of plasma concentrations with appropriate calibrators and controls using a chromogenic Factor Xa assay.[76] Plasma concentrations of dabigatran can be quantified using the HEMOCLOT dilute thrombin time assay.[77]

The half-life of direct OACs is much shorter than that of traditional anticoagulants, such as VKAs, but physicians remain concerned about the lack of specific reversal agents for the direct OACs to be used when, for example, a patient is bleeding. However, a universal Factor Xa inhibitor antidote[78] and neutralising fragment antibodies[79] are in development. When an overdose is suspected, administration of activated charcoal may be considered. In cases of mild or local bleeding, the next dose should be delayed or treatment discontinued as appropriate, and local compression is suggested. In cases of severe or life-threatening bleeding, administration of blood products is also recommended.[11 72 80] Limited clinical data support the suggestion that dialysis may be used to remove dabigatran at least partially from the blood[81]; however, owing to high plasma protein binding, rivaroxaban is unlikely to be dialysable. If bleeding cannot be controlled by these measures, administration of specific procoagulant reversal agents (prothrombin complex concentrate (PCC), activated PCC or recombinant Factor VIIa) should be considered. These suggestions are based on minimal clinical and non-clinical data.[11 72 80] Further studies of such potential reversal agents are required before these human plasma-derived products can be used routinely in clinical practice.

Managing the switch to and from other anticoagulants

Patients can be started on direct OAC treatment immediately after diagnosis of the appropriate indication; therefore, switching from one anticoagulant to another is rarely required. For patients with a condition that is well controlled by VKA therapy, there is little reason to switch between anticoagulant treatments. However, situations may arise that call for switching medication. If a transition between treatments is required, it is important to adhere to product guidelines to maintain an optimal anticoagulant effect during transition.

For patients who are unable to maintain INR in the therapeutic range, it might be necessary or beneficial to switch to a direct OAC. Switching from VKA to a direct OAC is relatively simple; VKA therapy should be stopped and direct OAC therapy started when the INR reaches <2.0 for apixaban and dabigatran, and ≤2.5 for DVT and PE treatment and prevention of

recurrence and ≤3.0 for stroke prevention, for rivaroxaban. When switching from a direct OAC to warfarin, coadministration of both drugs is required during the transition due to the slow onset of action of VKAs: continue coadministration until the INR is ≥2.0. INR measurement is best performed at the time of trough direct OAC concentration (ie, immediately before the next dose is due) to minimise any interference by the direct OAC on the measurement.[11 46 58]

Requirements for switching from a direct OAC to a parenteral anticoagulant are rare. One example might be the diagnosis of cancer, for which the recommended antithrombotic treatment is LMWH. Parenteral anticoagulants should be started at the next scheduled dose of rivaroxaban or apixaban. In the case of dabigatran, the parenteral anticoagulant should be withheld until 12 h after the final dose of dabigatran was administered. For the conversion from a parenteral anticoagulant, the first dose of direct OAC should be administered 0–2 h prior to the next scheduled dose of parenteral anticoagulant. In the case of continuously administered parenteral anticoagulants such as intravenous UFH, the first dose of apixaban, dabigatran or rivaroxaban should be administered at the time of discontinuation of parenteral anticoagulant treatment.[11 46 58]

In clinical practice, it is rare to switch from one direct OAC to another. One review suggests that, when converting from one direct OAC to another, the new treatment should begin at the next scheduled dose; however, in certain circumstances, for example switching from rivaroxaban to dabigatran in patients with CrCl 30–50 mL/min, rivaroxaban should be started 2–4 days after the final dose of dabigatran.[72]

CONCLUSIONS

The approval of the direct OACs represents an exciting new development in the treatment of thromboembolic disease that addresses many of the limitations of traditional anticoagulants. To successfully use the direct OACs in clinical practice, physicians must evaluate renal function and comedication use. They must also provide essential information about the benefits and side-effects of these agents, encourage patient adherence and, if necessary, monitor patient compliance. Implementation of direct OACs in hospital settings will provide clinical benefits to patients over traditional anticoagulants and will simplify treatment across a breadth of thromboembolic diseases.

Main messages

- Direct oral anticoagulants, which address many of the limitations of traditional anticoagulants, have been successfully studied for the prevention and treatment of a number of thromboembolic disorders.
- Effective use of these agents in clinical practice requires evaluation of renal function and co-medication use, together with patient education on benefits and risks and the importance of adherence to treatment.
- Implementation of direct oral anticoagulants will provide clinical benefits to patients and will simplify treatment.

Current research questions

- How will the largely positive results of clinical studies with the direct oral anticoagulants translate into real-world practice?
- What is the clinical utility of prohaemostatic agents, such as prothrombin complex concentrates, in the management of life-threatening bleeding associated with direct oral anticoagulants?
- In the absence of routine coagulation monitoring, how should patients receiving direct oral anticoagulants be integrated into existing protocols to ensure appropriate follow-up?

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Self assessment questions

Answer true (T) or false (F) to the below,

1. Renal function should not be determined before administration of direct OACs.
2. Direct OACs should not be used in pregnant individuals.
3. Routine measurement of anticoagulation intensity is recommended for all OACs.
4. All patients receiving VKA therapy should be switched to a direct OAC.
5. Rivaroxaban requires dose adjustment based on age, sex and weight.

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Answers

1. False
2. True
3. False
4. False
5. False