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REVIEW

Direct oral anticoagulants: key considerations for use to prevent stroke in patients with nonvalvular atrial fibrillation

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Abstract: Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. Strokes that occur as a complication of AF are usually more severe and associated with a higher disability or morbidity and mortality rate compared with non-AF-related strokes. The risk of stroke in AF is dependent on several risk factors; AF itself acts as an independent risk factor for stroke. The combination of effective anticoagulation therapy, risk stratification (based on stroke risk scores, such as $CHADS_2$ and CHA_2DS_2-VASc), and recommendations provided by guidelines is essential for decreasing the risk of stroke in patients with AF. Although effective in preventing the occurrence of stroke, vitamin K antagonists (VKAs; eg, warfarin) are associated with several limitations. Therefore, direct oral anticoagulants, such as apixaban, dabigatran etexilate, edoxaban, and rivaroxaban, have emerged as an alternative to the VKAs for stroke prevention in patients with nonvalvular AF. Compared with the VKAs, these agents have more favorable pharmacological characteristics and, unlike the VKAs, they are given at fixed doses without the need for routine coagulation monitoring. It remains important that physicians use these direct oral anticoagulants responsibly to ensure optimal safety and effectiveness. This article provides an overview of the existing data on the direct oral anticoagulants, focusing on management protocols for aiding physicians to optimize anticoagulant therapy in patients with nonvalvular AF, particularly in special patient populations (eg, those with renal impairment) and other specific clinical situations.

Keywords: direct oral anticoagulants, nonvalvular atrial fibrillation, rivaroxaban, stroke prevention, warfarin

Introduction

Atrial fibrillation (AF) is associated with substantial morbidity and mortality, mainly owing to the potential for thrombus formation and emboli that may occlude cerebral vessels.[1,2] Based on data from a large European population-based study, the overall prevalence of AF is 5.5%; prevalence increases with age, rising from 0.7% in people aged 55–60 years to 17.8% in those aged ≥85 years.[3] Because it is predominantly a disease of the elderly, the overall prevalence of AF is predicted to more than double by 2050, driven by the aging population.[3–5]

Approximately 15% of all strokes are associated with AF, and patients with AF have an approximately fivefold increase in the incidence of stroke compared with patients without AF.[1,2] Furthermore, strokes that occur in patients with AF are more severe than those in patients without AF, as demonstrated by the higher rates of death and the greater functional deficit associated with AF-related stroke.[6,7]

Optimal risk stratification plays a key role in the identification of patients with nonvalvular AF who have an elevated risk of stroke and would benefit from

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anticoagulant therapy. Factors associated with increased risk of stroke include prior thromboembolism, age ≥65 years, hypertension, congestive heart failure, impaired left ventricular systolic function, diabetes, female sex, and prior myocardial infarction (MI).[8–11] Several stroke risk scores exist: the most commonly used are $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes, and Stroke or transient ischemic attack [TIA] previous event [2 points]) and CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 years [2 points], Diabetes, Stroke or TIA previous event/thromboembolism [2 points], Vascular disease, Age 65–74 years, and Sex category [female]). The latter score was developed from the former to take into account important risk factors such as vascular disease, age, and sex (Table 1).[10,12,13]

To reduce the likelihood of stroke, oral anticoagulant therapy is recommended in all patients with AF who have additional stroke risk factors. A recent epidemiological study looking at anticoagulant use in patients with AF concluded that just 16% had no associated risk factors (ie, had a $CHADS_2$ score of 0).[14] This suggests that most patients with AF should be considered for anticoagulation; however, more than one-third of eligible patients received no form of anticoagulation.[14] The vitamin K antagonists (VKAs) are substantially more effective than antiplatelet therapy for stroke prevention: data from nine randomized trials comparing VKAs with acetylsalicylic acid (ASA) in patients with nonvalvular AF showed that VKAs were significantly more effective in preventing stroke (39% relative risk reduction).[15,16] Even in an elderly cohort (≥75 years of age), warfarin resulted in a significantly lower number of strokes with no appreciable increase in bleeding rates compared with ASA (1.4% with warfarin versus 1.6% with ASA).[17] VKA therapy has also been shown to have greater efficacy than dual antiplatelet therapy (DAPT; ASA plus clopidogrel) for stroke prevention in high-risk patients with AF (72% risk reduction) without a significant increase in major bleeding.[18] Therefore, the European Society of Cardiology (ESC) 2012 updated guidelines advise that treatment with ASA and clopidogrel should be reserved for patients in whom warfarin is considered unsuitable.[8]

Although the efficacy of VKAs for stroke reduction in patients with AF is well established,[16] these anticoagulants have several limitations, including a slow onset of action, a narrow therapeutic window, a high variability in dose response (influenced by patients' genetic background and other factors), numerous food and drug interactions, and the need for frequent coagulation monitoring and dose adjustment.[19–21] As a result, it is challenging to use VKAs in clinical practice, prompting the development of direct oral anticoagulants.

The direct oral anticoagulants include the direct Factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the direct thrombin inhibitor dabigatran, all of which can be administered as fixed doses, delivering predictable anticoagulation.[22] Apixaban, rivaroxaban, and dabigatran have been approved in Europe and the US for stroke prevention in AF, treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent venous thromboembolism (VTE).[23–25] Dabigatran is approved in Europe, and

Table 1 $CHADS_2$ and CHA_2DS_2-VASc stroke risk scoring systems and adjusted stroke rates based on $CHADS_2$ and CHA_2DS_2-VASc scores

	Stroke risk scoring systems		Adjusted stroke rate based on $CHADS_2$ score		Adjusted stroke rate based on CHA_2DS_2-VASc score	
	$CHADS_2$ scoring system	CHA_2DS_2-VASc scoring system	$CHADS_2$ score	Adjusted stroke rate (%/year)	CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)
Congestive heart failure	1	1	0	1.9	0	0
Hypertension	1	1	1	2.8	1	1.3
Age ≥75 years	1	2	2	4.0	2	2.2
Diabetes	1	1	3	5.9	3	3.2
Previous stroke or TIA	2	2	4	8.5	4	4.0
Vascular disease	–	1	5	12.5	5	6.7
Age, 65–74 years	–	1	6	18.2	6	9.8
Female sex	–	1	–	–	7	9.6
Maximum score	6	9	–	–	8	6.7
	–	–	–	–	9	15.2

Note: Data from Gage et al,[10,12] Lip et al,[13] and Camm et al.[15]

Abbreviations: $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and Stroke or TIA previous event (2 points); CHA_2DS_2-VASc, Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke or TIA previous event/thromboembolism (2 points), Vascular disease, Age 65–74 years, and Sex category (female); TIA, transient ischemic attack.

rivaroxaban and apixaban are approved in both Europe and the US for the prevention of VTE after elective hip or knee replacement surgery.[23–25] Rivaroxaban, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, is additionally approved in Europe for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) event with elevated cardiac biomarkers.[25] At present, edoxaban is approved in Japan (in several indications) and in the US for the prevention of stroke in patients with nonvalvular AF and for the treatment of VTE;[26] it is also under review by the European Medicines Agency (EMA) for approval in Europe.

This review will summarize the current treatment options and recommendations for the prevention of stroke in patients with nonvalvular AF, with an emphasis on the direct oral anticoagulants, highlighting important considerations regarding their use in high-risk patients and offering practical advice for clinical scenarios often encountered by the practicing physician.

Anticoagulation and stroke prevention

Current guidelines recommend anticoagulants over other antiplatelet therapies for the prevention of stroke in patients with AF with one or more risk factors.[8,9,15,27] The pivotal clinical studies of the direct oral anticoagulants for stroke prevention in patients with AF are presented below, along with the relevant properties of these agents.

Apixaban, dabigatran, edoxaban, and rivaroxaban for stroke prevention in nonvalvular atrial fibrillation

Pharmacodynamic and pharmacokinetic properties

The pharmacological profiles of the direct oral anticoagulants are more favorable than those of VKAs, such as warfarin. These novel agents target a single clotting factor (Factor Xa [apixaban, edoxaban, and rivaroxaban] or thrombin [dabigatran]) and, compared with warfarin, they have a faster onset of action (time to peak concentration: 0.5–4 hours versus 36–72 hours), shorter half-lives (5–17 hours versus 20–60 hours), and considerably fewer food and drug interactions (Table 2).[28–31] Therefore, these agents can be administered at fixed doses without a need for routine coagulation monitoring.[19,20]

Efficacy and safety in Phase III clinical studies

Large Phase III studies have investigated the efficacy and safety of apixaban, dabigatran, edoxaban, and rivaroxaban, compared with warfarin or ASA, in patients with nonvalvular AF. These include ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation), AVERROES (Apixaban VERsus acetylsalicylic acid to pRevent stroke in atrial fibrillation patients who

Table 2 Characteristics of direct oral anticoagulants compared with those of warfarin

Characteristics	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Bioavailability	>95%	~50% for doses up to 10 mg	~7%	>80% for 10 mg dose (regardless of food intake) and 20 mg dose (taken with food); 66% for 20 mg dose (under fasting conditions)	~62% for 60 mg dose
Time to peak activity	24–36 hours	3–4 hours	0.5–2 hours	2.0–4 hours	1–2 hours for 10–150 mg single dose
Half-life	20–60 hours	~12 hours	11–14 hours	5–9 hours (young individuals); 11–13 hours (elderly individuals)	6–11 hours for 10–150 mg single dose
Dosing frequency in AF	Once daily	Twice daily	Twice daily	Once daily	Once daily
Drug interactions	Numerous drugs including substrates of CYP2C9, CYP3A4, and CYP1A2; various foods	Strong inhibitors/inducers of both CYP3A4 and P-gp	Strong P-gp inhibitors and inducers	Strong inhibitors of both CYP3A4 and P-gp; strong CYP3A4 inducers	Strong P-gp inhibitors
Renal elimination	<1%	~27%	85%	66% of the dose undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated via the hepatobiliary route. The final 33% of the dose undergoes direct renal excretion	~50%

Note: Data from Bristol-Myers Squibb, Pfizer,[23] Boehringer Ingelheim International GmbH,[24] Bayer Pharma AG,[25] Daiichi Sankyo Inc.,[26] Eriksson et al,[28] Harder,[30] Verma and Brighton,[31] Stampfuss et al,[94] Matsushima et al,[95] and Mendell et al.[96]
Abbreviations: AF, atrial fibrillation; CYP, cytochrome P450; P-gp, P-glycoprotein.

have failed Or are unsuitable for vitamin K antagoniSt treatment), RE-LY (Randomized Evaluation of Long-term anticoagulation therapY), ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction Study 48), and ROCKET AF (Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation).[32–36] The design and main efficacy and safety outcomes of these studies are shown in Table 3. No head-to-head comparison trials of the direct oral anticoagulants have been conducted to date.

In the studies comparing the direct oral anticoagulants with warfarin, high-dose dabigatran (150 mg twice daily [bid]), and apixaban were shown to be superior to warfarin for the prevention of stroke and systemic embolism in the intention-to-treat population;[32,34,37] in this setting, rivaroxaban, low-dose dabigatran (110 mg bid), and both doses of edoxaban (60 mg once daily [od] and 30 mg od) were shown to be noninferior to warfarin (Table 4).[32,33,36,37] The AVERROES study was terminated early owing to a clear benefit of apixaban over ASA for the prevention of stroke and systemic embolism.[35]

Different major bleeding definitions were used in the Phase III clinical studies of the direct oral anticoagulants, and enrolled patients had different baseline bleeding risks. Nonetheless, the direct oral anticoagulants were associated with a similar or lower incidence of major bleeding compared with warfarin (Table 4)[32–34,36–38] or ASA.[35] The risk of intracranial hemorrhage (ICH; the most serious complication of anticoagulation therapy[39]) was 33%–70% lower in patients treated with a direct oral anticoagulant than in those treated with warfarin (Table 4).[32–36,38,40] Fatal bleeding rates were also lower in patients treated with apixaban, rivaroxaban, edoxaban, and low-dose (110 mg bid) dabigatran compared with patients treated with warfarin; similar rates of fatal bleeding were seen in patients treated with high-dose (150 mg bid) dabigatran (Table 4).[33,34,36,41] In the AVERROES study comparing apixaban with ASA, rates of ICH and fatal bleeding were comparable in both treatment groups.[35]

Table 3 Study designs for ARISTOTLE, AVERROES, RE-LY, ENGAGE AF-TIMI 48, and ROCKET AF

	ARISTOTLE[34]	AVERROES[35]	RE-LY[32]	ENGAGE AF-TIMI 48[36]	ROCKET AF[33]
Study drug	Apixaban	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Comparator	Warfarin	ASA	Warfarin (open-label)	Warfarin	Warfarin
Study design					
Blinding	Double-blind, double-dummy	Double-blind, double-dummy	Blinded dabigatran (two doses)	Double-blind, double-dummy	Double-blind, double-dummy
Statistical objective	Noninferiority	Superiority	Noninferiority	Noninferiority	Noninferiority
Doses studied	5 mg bid[a]	5 mg bid	110 mg bid and 150 mg bid	30 mg od and 60 mg od[b]	20 mg od[c]
Number of risk factors	≥1	≥1	≥1	≥1	≥2
Study outcomes					
Primary efficacy	Composite of stroke and systemic embolism	Composite of stroke and systemic embolism	Composite of stroke and systemic embolism	Composite of stroke and systemic embolism	Composite of stroke and systemic embolism
Principal safety	Major bleeding[d]	Major bleeding[d]	Major bleeding[e]	Major bleeding[f]	Major[g] and nonmajor clinically relevant bleeding[h]

Notes: [a]A reduced dose of apixaban (2.5 mg bid) was used in patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL; [b]both doses of edoxaban were halved if the patients had CrCl of 30–50 mL/min; body weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone at randomization or during the study; [c]a reduced dose of rivaroxaban (15 mg od) was used in patients with moderate renal impairment (CrCl 30–49 mL/min); [d]defined according to the criteria of the ISTH as clinically overt bleeding accompanied by a decrease in hemoglobin level of ≥2 g/dL over a 24-hour period or transfusion of ≥2 units of whole blood or red cells, occurring at a critical site or resulting in death; [e]defined as a reduction in hemoglobin level of ≥20 g/L, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ; [f]defined as clinically overt bleeding associated with fatal outcome, involving a critical site, or clinically overt bleeding associated with a fall in hemoglobin concentration of ≥2 g/dL adjusted for blood transfusions or a fall in hematocrit of ≥6.0% adjusted for blood transfusions; [g]defined as clinically overt bleeding associated with fatal outcome, involving a critical site, or clinically overt bleeding associated with a fall in hemoglobin concentration of ≥2 g/dL, or leading to transfusion of ≥2 units of packed red blood cells or whole blood; [h]defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician (visit or telephone call), temporary cessation (ie, by delaying the next administration) of study drug, pain, or impairment of daily activities.

Abbreviations: ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembolIc Events in atrial fibrillation; ASA, acetylsalicylic acid; AVERROES, Apixaban VERsus acetylsalicylic acid to pRevent stroke in atrial fibrillation patients who have failed Or are unsuitablE for vitamin K antagoniSt treatment; bid, twice daily; CrCl, creatinine clearance; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction Study 48; ISTH, International Society on Thrombosis and Haemostasis; od, once daily; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF, Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

Table 4 Summary of key findings from the four Phase III outcome trials of rivaroxaban, apixaban, edoxaban, and dabigatran versus warfarin in patients with atrial fibrillation

Trial name and direct OAC	ARISTOTLE[34]	RE-LY[32,37,38,41]		ENGAGE AF-TIMI 48[36]		ROCKET AF[33]
	Apixaban	Dabigatran		Edoxaban		Rivaroxaban
Direct OAC dose	5 mg bid[a]	110 mg bid	150 mg bid	30 mg od[b]	60 mg od[b]	20 mg od[c]
Patient characteristics						
Total number of patients	18,201	18,113		21,105		14,264
Median age, years	70 vs 70	71 vs 72[d]	72 vs 72[d]	72 vs 72	72 vs 72	73 vs 73
Mean $CHADS_2$ score	2.1 vs 2.1	2.1 vs 2.1	2.2 vs 2.1	2.8 vs 2.8	2.8 vs 2.8	3.5 vs 3.5
Prior stroke or TIA, %	19 vs 20	20 vs 20	20 vs 20	29 vs 28	28 vs 28	55 vs 55
Mean TTR (warfarin patients), %	62	64		65		55
Main outcomes (relative risk vs warfarin)						
Stroke or systemic embolism[e]	0.79 (0.66–0. 95)[f]	0.89 (0.73–1.09)	0.65 (0.52–0.81)	1.13 (0.93–0.34)[g]	0.87 (0.73–1.04)[g]	0.88 (0.75–1.03)[h]
Major bleeding[i]	0.69 (0.60–0.80)[f]	0.80 (0.70–0.93)	0.94 (0.82–1.08)	0.47 (0.41–0.55)	0.80 (0.71–0.91)	1.04 (0.90–1.20)
Intracranial bleeding[i]	0.42 (0.30–0.58)[f]	0.30 (0.19–0.45)	0.41 (0.28–0.60)	0.30 (0.21–0.43)	0.47 (0.34–0.63)	0.67 (0.47–0.93)
Gastrointestinal bleeding[i]	0.89 (0.70–1.15)[f]	1.08 (0.85–1.38)	1.48 (1.18–1.85)	0.67 (0.53–0.83)	1.23 (1.02–1.50)	3.15% vs 2.16%; $P<0.001$
Fatal bleeding[i]	34 vs 55 patients[e]	0.58 (0.35–0.97)	0.7 (0.43–1.14)	0.35 (0.21–0.57)	0.55 (0.36–0.84)	0.50 (0.31–0.79)

Notes: [a]2.5 mg bid in patients with ≥2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL; [b]halving of dose if CrCl 30–50 mL/min; body weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone; [c]15 mg od in patients with CrCl 30–49 mL/min; [d]mean; [e]ITT population; [f]hazard ratio (95% CI); [g]the primary efficacy analysis was prespecified to be performed in the on-treatment modified ITT population set that includes all randomized subjects who received ≥1 dose of randomized study drug. The treatment period was defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of the double-blind therapy; [h]the primary efficacy analysis was prespecified to be performed in the per-protocol population, which included all patients who received ≥1 dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days after discontinuation; [i]safety population.

Abbreviations: ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembolLic Events in Atrial Fibrillation; bid, twice daily; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and Stroke or TIA previous event (2 points); CI, confidence interval; CrCl, creatinine clearance; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction Study 48; ITT, intent-to-treat; OAC, oral anticoagulant; od, once daily; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF, Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischemic attack; TTR, time in therapeutic range for international normalized ratio.

The incidence of major gastrointestinal (GI) bleeding varied with the use of the different direct oral anticoagulants. Compared with warfarin, a lower incidence of major GI bleeding was observed in the low-dose (30 mg od) edoxaban group; a similar incidence was observed in the apixaban and low-dose dabigatran (110 mg bid) groups; and a higher incidence was observed in patients treated with high-dose (150 mg bid) dabigatran, rivaroxaban, or high-dose edoxaban (60 mg od) (Table 4).[32–34,36,38] Similar rates of major GI bleeding were observed between patients treated with apixaban and ASA.[35]

Non-bleeding-related adverse events occurred at a similar rate in direct oral anticoagulant-treated and warfarin-treated patients in the ROCKET AF, ARISTOTLE, and ENGAGE studies.[33,34,36] In the RE-LY study, a significantly greater incidence of dyspepsia was observed in dabigatran-treated patients compared with warfarin-treated patients; rates of other non-bleeding-related adverse events were similar in the two treatment groups.[32]

Current guideline recommendations for stroke prevention

The ESC 2012 guidelines state a preference for the use of the direct oral anticoagulants approved for stroke prevention in patients with nonvalvular AF, given that they offer better efficacy, safety, and convenience profiles compared with VKAs.[8] The guidelines do not recommend a single direct anticoagulant over another, because direct comparisons are not available. Further guidance about necessary dose adjustments based on age, the use of concomitant interacting drugs, bleeding risk, and renal function is also given.[8] A summary of the recommendations for the use of the direct oral anticoagulants for the prevention of stroke in patients with AF is shown in Table 5 as per their respective European approved Summaries of Product Characteristics (SmPCs).[23–25]

Optimizing patient management

Although the most recent guidelines for stroke prevention in patients with AF are intended to guide the optimal care of patients, particularly when the selection of treatment is based on patient demographics (eg, stroke or bleeding risk), an understanding of the pharmacological characteristics of the drug and the implications for management are also important. Some of the main management issues, together with the recommendations provided by the European SmPC for each direct oral anticoagulant, are discussed below.[23–25]

Table 5 Summary of guidance in agreement with the Summary of Product Characteristics approved by the European Medicines Agency for use of direct oral anticoagulants for stroke prevention in patients with atrial fibrillation

Recommended dose	Apixaban[23]	Dabigatran[24]	Rivaroxaban[25]
	5 mg bid	**150 mg bid**	**20 mg od**
Dose adjustments	2.5 mg bid for patients with CrCl 15–29 mL/min or with serum creatinine ≥1.5 mg/dL associated with age ≥80 years or with body weight ≤60 kg	110 mg bid in patients 75–80 years with low thromboembolic risk and high risk of bleeding, or ≥80 years with CrCl 30–50 mL/min and high risk of bleeding, or receiving the strong P-gp inhibitor verapamil	15 mg od for CrCl 15–49 mL/min
Contraindications	Clinically significant active bleeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk Lesion or condition at significant risk of major bleeding Hypersensitivity to the active substance or excipients Concomitant treatment with any other anticoagulant agent[a]	Active clinically significant bleeding Hepatic impairment or liver disease expected to have any impact on survival Lesion or condition causing significant risk of major bleeding Hypersensitivity to the active substance or excipients Concomitant treatment with any other anticoagulant agent[a] CrCl <30 mL/min Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, and dronedarone (strong P-gp inhibitors) Prosthetic heart valves requiring anticoagulant treatment[b]	Clinically significant active bleeding Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (including Child–Pugh B and C) Lesion or condition at significant risk of major bleeding Hypersensitivity to the active substance or excipients Concomitant treatment with any other anticoagulant agent[a] Pregnancy or breastfeeding
Not recommended in:	Pregnant women Patients with: • CrCl <15 mL/min • Prosthetic heart valves requiring anticoagulant treatment • Severe hepatic impairment Patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (eg, ketoconazole, itraconazole, voriconazole, and posaconazole) and HIV protease inhibitors (eg, ritonavir)	Patients with raised liver enzymes indicative of hepatic impairment (>2 ULN) Patients receiving concomitant treatment with HIV protease inhibitors (eg, ritonavir) Patients receiving concomitant treatment with the P-gp inhibitor tacrolimus Patients receiving concomitant treatment with P-gp inducers (eg, rifampicin, St John's wort, carbamazepine, or phenytoin) – coadministration with dabigatran should be avoided	Children <18 years old Patients with: • CrCl <15 mL/min • Prosthetic heart valves requiring anticoagulant treatment[c] • Increased bleeding risk (eg, genetic bleeding disorders, uncontrolled severe hypertension) Patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole, and posaconazole) or HIV protease inhibitors (eg, ritonavir) Patients receiving dronedarone – coadministration with rivaroxaban should be avoided
Drugs that should be used with caution with direct OACs (all patients)	Strong inducers of both CYP3A4 and P-gp (eg, rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort) NSAIDs, including ASA	Drugs affecting hemostasis by inhibition of platelet aggregation (eg, ASA, NSAIDs, clopidogrel)[d] Mild to moderate P-gp inhibitors (eg, amiodarone, posaconazole, quinidine, verapamil, and ticagrelor) Selective SSRIs or selective SNRIs[d]	NSAIDs (including ASA) and platelet aggregation inhibitors Strong CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, or St John's wort) should be avoided unless the patient is closely observed for signs and symptoms of thrombosis

Drugs requiring caution during concomitant treatment in patients with renal impairment	Close clinical surveillance is recommended in patients with mild to moderate renal impairment when dabigatran is combined with mild to moderate P-gp inhibitors (eg, amiodarone, quinidine, verapamil, and clarithromycin)	Moderate or potent inhibitors of CYP3A4 (eg, fluconazole, clarithromycin) Moderate inhibitors of both CYP3A4 and P-gp (eg, erythromycin)	
Switching from a VKA to a direct OAC	Discontinue warfarin or other VKA therapy and start apixaban at INR <2.0	Discontinue VKA and start dabigatran at INR <2.0	Discontinue VKA and start rivaroxaban at INR ≤3.0[e]
Switching to a VKA from a direct OAC	When converting patients to a VKA, continue apixaban for at least 2 days after beginning VKA therapy. After 2 days of coadministration, obtain an INR before the next scheduled dose of apixaban, and continue coadministration until the INR is ≥2.0	VKA starting time should be based on CrCl If CrCl is ≥50 mL/min, start VKA 3 days before discontinuing dabigatran If CrCl is 30–49 mL/min, start VKA 2 days before discontinuing dabigatran	VKA and rivaroxaban should be given concurrently until the INR is ≥2.0; standard initial VKA dosing should be given for the first 2 days of the conversion period, followed by INR-guided VKA dosing; INR should not be tested earlier than 24 hours after the previous rivaroxaban dose

Notes: [a]Except under specific situation of switching anticoagulants or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; [b]the use of dabigatran in patients with mechanical heart valves has been shown to increase the rates of thromboembolic and bleeding complications compared with warfarin; this observation led to the premature termination of the Phase II RE-ALIGN trial;[97] [c]not recommended because there is a lack of safety and efficacy studies with this agent in patients with prosthetic heart valves; [d]concomitant treatment with dabigatran and NSAIDs, antiplatelet agents, SSRIs, or SNRIs increases the risk of major bleeding and, therefore, requires careful risk assessment. Dabigatran should be used in patients on these medications only if the potential benefit outweighs the bleeding risks; [e]for patients being treated for a venous thromboembolism and switching from a VKA to rivaroxaban, the VKA should be discontinued and rivaroxaban treatment started when the INR is ≤2.5.

Abbreviations: ASA, acetylsalicylic acid; bid, twice daily; CrCl, creatinine clearance; CYP, cytochrome P450; HIV, human immunodeficiency virus; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; od, once daily; P-gp, P-glycoprotein; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; UFH, unfractionated heparin; ULN, upper level of normal; VKA, vitamin K antagonist.

Patients with renal impairment

Renal impairment is an important consideration in patients with AF who are receiving apixaban, dabigatran, or rivaroxaban and will also be the case for those receiving edoxaban when this agent gains approval, because all four agents are eliminated renally (to a greater or lesser extent) (Table 2). Renal excretion accounts for approximately 27% of total clearance of apixaban.[23] For rivaroxaban, one-third of the administered dose undergoes direct renal excretion as unchanged active substance in the urine.[25] Approximately 35%–39% of edoxaban is eliminated via renal excretion.[42] Dabigatran is eliminated primarily in the urine, and renal clearance of dabigatran accounts for 85% of total clearance after intravenous administration.[24] Varying degrees of renal impairment will, therefore, lead to increased drug exposure, which may increase the risk of bleeding.[30]

In the Phase III trials of direct oral anticoagulants, patients with nonvalvular AF and severe renal impairment (creatinine clearance [CrCl] <25 mL/min [ARISTOTLE] or <30 mL/min [ENGAGE AF-TIMI 48, RE-LY, and ROCKET AF]) were excluded.[32–34,36,43] Dose adjustments were made for patients who had moderate renal impairment in the studies of the three Factor Xa inhibitors. In ARISTOTLE, apixaban 2.5 mg bid, rather than 5 mg bid, was allocated to patients expected to have a higher drug exposure, namely, any patients with two of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL (133 µmol/L).[34] Patients in the ENGAGE AF-TIMI 48 trial were randomized to either the edoxaban 30 or 60 mg dose groups. A halving of both doses occurred in patients who had any one of the following, whether at randomization or at any time during the study: CrCl 30–50 mL/min; body weight ≤60 kg; or receiving verapamil, quinidine, or dronedarone.[36] In ROCKET AF, patients with CrCl 30–49 mL/min received rivaroxaban 15 mg od, instead of the 20 mg od dose given to patients with noncompromised renal function.[33] Despite 19% of patients in RE-LY having a CrCl <50 mL/min, no dose adjustment was made.[32]

The corresponding percentages of patients with reduced renal function were approximately 15% (CrCl >30–50 mL/min) in ARISTOTLE; 19% and 20% for low- and high-dose edoxaban (CrCl ≤50 mL/min), respectively, in ENGAGE AF-TIMI 48; and 21% (CrCl, 30–49 mL/min) in ROCKET AF.[33,34,36] In the apixaban and rivaroxaban studies, and irrespective of treatment assignment, patients with renal impairment had numerically higher rates of stroke or major bleeding events than patients without renal impairment.[32,34,36,43] In ARISTOTLE, for patients without renal impairment

(CrCl >80 mL/min) treated with apixaban, major bleeding was 1.5% per year; this rate increased to 2.5% and 3.2% per year for those with mild (CrCl >50–80 mL/min) and moderate (CrCl >30–50 mL/min) or severe (CrCl ≤30 mL/min) renal impairment, respectively.[34] Apixaban was associated with significantly fewer major bleeding events in patients with moderate or severe renal impairment compared with warfarin (P=0.03 for interaction).[34]

No data are yet available regarding the rates of stroke and major bleeding in patients with renal impairment receiving edoxaban, although the reduction in major bleeding with edoxaban compared with warfarin was greater among dose-reduced patients than among those who did not receive a dose reduction.[36] However, the recent US Food and Drug Administration (FDA) approval of edoxaban limits its use to patients with a CrCl ≤95 mL/min on the basis that patients with a CrCl >95 mL/min had an increased rate of ischemic stroke with high-dose edoxaban (60 mg od) compared with patients treated with warfarin.[26]

In RE-LY, the major bleeding rates for dabigatran 110 and 150 mg were 1.53% and 2.09% per year, respectively, in patients with no renal impairment (CrCl >80 mL/min); 2.89% and 3.33% per year, respectively, for patients with mild renal impairment (CrCl 50–79 mL/min); and 5.29% and 5.44% per year, respectively, in patients with moderate (CrCl <50 mL/min) renal impairment.[41] Major bleeding in ROCKET AF was similar for the rivaroxaban and warfarin groups (3.6% versus 3.4% per year; P=0.58);[33] in a subgroup analysis of patients with renal impairment, the rates of major bleeding for rivaroxaban and warfarin were 3.39% versus 3.17% per year (CrCl ≥50 mL/min) and 4.49% versus 4.70% per year (CrCl 30–49 mL/min), respectively.[43] The efficacy and safety profiles of apixaban, dabigatran, and rivaroxaban versus warfarin were consistent across subgroups representing decreasing renal function.[32,35,41,43] These results are supported by a recently published meta-analysis based on the results of the Phase III clinical trials of the direct oral anticoagulants for stroke prevention and VTE treatment, which has shown that, in patients with renal insufficiency, recommended doses of direct oral anticoagulants are noninferior and relatively safe compared with conventional anticoagulants.[44]

Because of the potential for raised plasma drug levels in patients with severe renal impairment (CrCl <30 mL/min), the use of dabigatran is contraindicated in these patients.[24] Rivaroxaban should be used with caution in patients with CrCl of 15–29 mL/min, and rivaroxaban and apixaban are not recommended in patients with CrCl <15 mL/min.[23,25] Although no dose adjustment is required in patients with mild renal impairment (CrCl 50–80 mL/min), reduced dosing is necessary with increasing degrees of renal impairment and in patients with renal impairment at increased risk of bleeding (Table 5). Concomitant treatment with drugs that target the pathways of elimination may further increase bleeding risk. A full listing of the drugs requiring caution during concomitant treatment in patients with renal impairment is given in Table 5.[23–25] These drugs should be used in patients with renal impairment only if the potential benefits outweigh the risks.

The ESC 2012 guidelines recommend assessing renal function using CrCl for patients on all direct oral anticoagulants, but especially for patients taking dabigatran, which has a high renal clearance.[8] Annual assessment of renal function is recommended, and patients with moderate renal impairment (CrCl 30–49 mL/min) should be assessed more regularly (2–3 times per year).[8] Renal function may be assessed more frequently if necessary, particularly for patients >75 years of age and in clinical situations in which renal function could decline or deteriorate, such as hypovolemia, urosepsis, or with initiation of potentially nephrotoxic agents.[8,24]

Patients with recent stroke

Subgroup analyses from Phase III trials showed that the favorable efficacy and safety evident in the main population was not significantly different for patients with previous stroke or TIA.[45–47] Nevertheless, the benefit of direct oral anticoagulants in patients with a recent stroke has not been established because the Phase III studies excluded patients who had had an acute stroke within 1–2 weeks of randomization or severe disabling stroke within 3–6 months of randomization.[33,48–50] Decisions about restarting anticoagulation in these patients remain challenging. A large systematic review involving 23,748 patients with acute ischemic stroke showed that restarting anticoagulation within the first few days of the stroke did reduce the incidence of recurrent stroke but increased symptomatic ICH.[51] Other studies have shown that there is no net benefit in terms of reducing recurrent stroke in the short term (12 days) or of morbidity/mortality in the long term (1 year).[52]

The practical guide from the European Heart Rhythm Association (EHRA) suggests that continuation with direct oral anticoagulants after ischemic stroke should be guided by the size of the infarct. As a rule of thumb, it is suggested that anticoagulants are recommenced 1 day after a TIA; 3 days after a small, nondisabling infarct; and 6 days after a moderate stroke.[53] After a large stroke, because the risks

of hemorrhagic transformation of the infarct are greater, anticoagulant therapy should be delayed for at least 2 weeks after the presenting event.[53,54] Evidence from community-based studies indicates that the risk of recurrence after stroke varies from 1.7% to 4.0% in the first 30 days.[55]

Patients undergoing cardioversion

Cardioversion increases the risk of thromboembolism, and anticoagulation is recommended before and after electrical or pharmacological cardioversion of AF.[15,56] To date, rivaroxaban is the only direct oral anticoagulant that has completed a Phase III clinical study in this indication. The X-VeRT study (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion) was an exploratory study in which patients were randomly assigned to rivaroxaban or VKA before undergoing early or delayed electrical or pharmacological cardioversion.[57] The primary efficacy outcome (a composite of stroke, TIA, peripheral embolism, MI, and cardiovascular death) occurred numerically less often in patients assigned to rivaroxaban than VKA (0.51% versus 1.02%; risk ratio: 0.5; 95% confidence interval: 0.15–1.73), and major bleeding rates were similar in both treatment arms (0.61% versus 0.80%; risk ratio: 0.76; 95% confidence interval: 0.21–2.67). Furthermore, the time between randomization and cardioversion was similar or shorter in patients assigned to rivaroxaban compared with VKA (early: median =1 [interquartile range: 1–2] versus 1 [1–3] days, P=0.628; delayed: 22 [21–26] versus 30 [23–42] days; $P<0.001$). Overall, the results of the X-VeRT study suggest that rivaroxaban is an effective and safe alternative to VKAs in patients with AF undergoing cardioversion and may allow for more prompt cardioversion.[57] Although planned cardioversion was an exclusion criterion in ROCKET AF, a small number of patients (285 patients) underwent cardioversion. The results of a subgroup analysis in this group of patients support those from the X-VeRT study; rates of stroke or systemic embolism, or death from any cause, were reported to be similar for patients treated with rivaroxaban or warfarin after cardioversion.[58]

In RE-LY, patients undergoing cardioversion were recommended to remain on dabigatran. Of 18,113 patients randomized, 7% had cardioversions. In these patients, the rate of stroke or systemic embolism was low, and major bleeding was infrequent in all patient groups.[32,59] Rates of stroke or systemic embolism were 0.77%, 0.30%, and 0.60%, and rates of major bleeding were 1.7%, 0.6%, and 0.6% in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively.[59] Rates of thromboembolism were similar for patients receiving conventional and transesophageal echocardiogram-guided cardioversions. These findings confirmed that dabigatran is a valid alternative to warfarin in patients requiring cardioversion.[59] In ARISTOTLE, a post hoc analysis of patients undergoing cardioversion reported that major cardiovascular events (including stroke or systemic embolism, MI, or death) after cardioversion are rare and comparable between patients treated with apixaban or warfarin.[60] The effectiveness of apixaban compared with VKAs in patients with nonvalvular AF undergoing early cardioversion is currently being investigated in the ongoing Phase IV clinical study, EMANATE.[61]

At the time the ESC guidelines on the management of patients with AF undergoing cardioversion were written, the only published study of a direct oral anticoagulant in this setting was the preliminary RE-LY post hoc analysis; therefore, only dabigatran (or VKA) was included in the recommendations.[8] The more recent EHRA practical guide, published in 2013 after the publication of preliminary results of post hoc analyses of patients undergoing cardioversion in the ROCKET AF and ARISTOTLE trials, suggests that cardioversion is acceptably safe in patients treated with any of the three approved direct oral anticoagulants, providing compliance can be reliably confirmed. If there are any doubts about compliance, transesophageal echocardiogram should be performed prior to the procedure to exclude the presence of left atrial thrombi.[53]

Patients with atrial fibrillation requiring concomitant antiplatelet therapy

The management of patients with AF who experience an ACS event and require percutaneous coronary intervention (PCI) with stenting is challenging because combined anticoagulant and antiplatelet treatment is warranted. At present, no data are available from the clinical trials of the direct oral anticoagulants in patients with AF undergoing PCI. ESC guidelines recommend VKA therapy (with a target international normalized ratio [INR] of 2.0–2.5) in combination with DAPT after PCI and stent placement.[15,62,63] However, since these guidelines have been published, management practices for patients with AF have significantly evolved with the approval of the direct oral anticoagulants, and newer-generation drug-eluting stents (which may be less thrombogenic) have been developed. In light of these changes, the ESC and EHRA, together with the European Association of Percutaneous Cardiovascular Interventions and European Association of Acute Cardiac Care, have recently published

a consensus document regarding the management of patients with AF and ACS (or stable coronary artery disease) who require PCI with stenting.[64] Specific recommendations for the duration of combined anticoagulant and single or dual antiplatelet therapy are given, dependent on a patient's stroke risk, their bleeding risk, and the clinical setting (elective PCI or urgent PCI owing to ACS).[64] Further details can be found in Table 6. Given that combination therapy of antiplatelet agents with a VKA or direct oral anticoagulant (at intensities used for stroke prevention) is associated with elevated risks of bleeding,[65–69] a lower-intensity anticoagulant regimen is recommended (target INR of 2.0–2.5 for VKAs; direct oral anticoagulants at the lower tested dose in AF trials [ie, apixaban 2.5 mg bid, rivaroxaban 15 mg od, dabigatran 110 mg bid]).[64] Additional recommendations include the use of proton pump inhibitors (to minimize the risk of GI bleeding, particularly when ASA is used), and the use of newer-generation drug-eluting stents over bare metal stents, especially in patients at a low risk of bleeding.[64]

In patients with AF undergoing PCI with stent placement, there is currently no information available to compare the elevated bleeding risk of combined therapy with an antiplatelet and a VKA versus combined therapy with an antiplatelet and a direct oral anticoagulant. Phase III clinical trials are ongoing in this setting. PIONEER-AF-PCI[70] is evaluating the safety of two different rivaroxaban regimens (2.5 mg bid or 15 mg od [10 mg od in patients with renal impairment]) compared with a VKA regimen; all patients will receive concomitant treatment with various combinations of DAPT or low-dose ASA or clopidogrel (or prasugrel or ticagrelor). In RE-DUAL PCI,[71] two doses of dabigatran (110 mg bid or 150 mg bid) plus single antiplatelet therapy are being

Table 6 Consensus recommendations for antithrombotic management of patients with atrial fibrillation after percutaneous coronary intervention

Hemorrhage risk	Clinical setting	Stroke risk[a]	Recommendations for antithrombotic therapy		
			Timing of treatment after PCI	Therapy	Details
Low or moderate (HAS-BLED ≤2)	Stable CAD (elective PCI)	Moderate	≥4 weeks <6 months	Triple therapy[b]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy[c]	Reduced-dose OAC + clopidogrel *or* Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
		High	≥4 weeks <6 months	Triple therapy[e]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel *or* Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
	ACS (urgent PCI)	Moderate or high	Up to 6th month	Triple therapy	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy[f]	Reduced-dose OAC + clopidogrel *or* Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
High (HAS-BLED ≥3)	Stable CAD (elective PCI)	Moderate	Up to 12th month	Dual therapy[c]	Reduced-dose OAC + clopidogrel
			Lifelong	Single therapy	Standard-dose OAC[d]
		High	4 weeks	Triple therapy[b]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel *or* Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
	ACS (urgent PCI)	Moderate or high	4 weeks	Triple therapy[e]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel *or* Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]

Notes: Unless specified, ASA dose is 75–100 mg/day and clopidogrel dose is 75 mg/day. Reduced-dose OAC refers to either a VKA with a target INR of 2.0–2.5 or direct OAC at the lowest tested dose in AF (apixaban 2.5 mg bid, rivaroxaban 15 mg od, or dabigatran 110 mg bid). Tailored guidance for patients with AF already on a reduced dose of direct OAC before a PCI is not given. [a]Stroke risk assessed via CHA_2DS_2-VASc; moderate risk is defined as a score of 1, high risk is defined as a score of ≥2; only male patients with AF undergoing PCI can be defined as moderate risk – female patients with AF undergoing PCI will have a CHA_2DS_2-VASc score of ≥2; [b]combination of reduced-dose OAC + clopidogrel 75 mg/day or dual antiplatelet therapy consisting of ASA 75 mg/day and clopidogrel 75 mg/day may be considered as an alternative; [c]dual antiplatelet therapy consisting of ASA 75 mg/day and clopidogrel 75 mg/day may be considered as an alternative; [d]in selected patients (eg, those with stenting of the left main proximal bifurcation, or recurrent myocardial infarctions), dual therapy with OAC and single antiplatelet therapy may be continued beyond 12 months; [e]combination of OAC and clopidogrel 75 mg/day may be considered as an alternative; [f]in selected patients at high stroke risk, continuation of triple therapy between 6 and 12 months may be considered. Data from Lip et al.[64]

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; bid, twice daily; CAD, coronary artery disease; CHA_2DS_2-VASc, Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke or transient ischemic attack previous event/thromboembolism (2 points), Vascular disease, Age 65–74 years, and Sex category (female); INR, international normalized ratio; OAC, oral anticoagulant; od, once daily; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist; HAS-BLED, Hypertension, Abnormal Liver Function, Stroke History, Bleeding Predisposition, Labile INRs, Elderly, Drugs Concomitantly.

compared with warfarin plus DAPT. Results of these studies are not expected until after 2016 and 2017, respectively.

Management of bleeding

All anticoagulants are associated with a risk of bleeding. Appropriate patient selection before initiating treatment with direct oral anticoagulants is therefore important to minimize the risk of bleeding events. Before the use of direct oral anticoagulants, standard bleeding risk stratification (eg, by HAS-BLED [Hypertension, Abnormal Liver, Stroke History, Bleeding Predisposition, Labile INRs, Elderly, Drugs] score [≥3]) enables identification of patients at high risk of bleeding (who must exert caution and need regular review) and may allow for correction of reversible risk factors associated with bleeding.[15] Several groups of patients are recognized to be at high risk of bleeding, including patients with congenital or acquired coagulation disorders, patients with ulcerative GI disease, or patients undergoing treatment with drugs that are also associated with an increased bleeding risk, such as antiplatelet agents.[24,25] For these high-risk patients, close clinical surveillance for overt bleeding (eg, regular measurement of hemoglobin and blood pressure) should be employed, and any decreases in hemoglobin or blood pressure should be investigated systematically.[24,25] This investigation should include assessment for occult bleeding (eg, in stools or urine).

Standard management of patients who develop major bleeding is to delay or discontinue the anticoagulant until the source of bleeding is established. Supportive treatment includes mechanical compression, surgical hemostasis, and blood volume or full blood replacements.[72] Additionally, coagulation tests may help to determine whether the bleeding is caused by an overdose or the timing of the most recent dose.[73]

Although the Phase III stroke prevention studies of the direct oral anticoagulants versus warfarin demonstrated an improved benefit–risk profile of direct oral anticoagulants in terms of reduced incidence of fatal bleeding and ICH,[32–36,38,40] concern remains among physicians because there are currently no specific reversal agents for the direct oral anticoagulants in emergency situations.[72,73] However, it should be remembered that, first, the reversal of the anticoagulant effects of warfarin using vitamin K is slow and of no use for the treatment of life-threatening bleeding;[72] therefore, nonspecific reversal agents, such as prothrombin complex concentrates, are administered together with vitamin K. Second, the antidote for low-molecular-weight heparins, protamine sulfate, can only partially counteract their anticoagulant effects.[74] Lastly, the short half-life of the direct oral anticoagulants means that time is often an effective "antidote." Nonetheless, specific reversal agents for the Factor Xa inhibitors (andexanet alfa) and dabigatran (idarucizumab) are currently under development and in Phase III clinical trials[75–77] to address the unmet need for reversal agents for the direct oral anticoagulants, and they are anticipated to become available in the near future.

In the event that a patient on a direct oral anticoagulant presents with life-threatening bleeding, off-label use of nonspecific reversal agents (including prothrombin complex concentrates, recombinant Factor VIIa, and Factor VIII inhibitor bypass activity) may be considered when all other measures have failed.[53] Preclinical studies (in vitro[78–80] and in animal models[81–86]) and a small number of Phase I/II clinical studies in healthy volunteers[87,88] have demonstrated the ability of these hemostatic agents to reverse some of the effects of the direct oral anticoagulants. However, clinical data regarding the use of prothrombin complex concentrates, recombinant Factor VIIa, and Factor VIII inhibitor bypass activity in patients presenting with bleeding events while receiving direct oral anticoagulants are limited because experience to date (in both clinical trials and real-world daily practice) suggests that most major bleeding events can be managed without the use of reversal agents.[89,90]

Switching anticoagulation

Management of the direct oral anticoagulants for transitioning to and from warfarin, as required by the patient's clinical situation or in the event of elective surgery (eg, orthopedic surgery or cosmetic surgery), involves an appreciation of the pharmacokinetics of the drugs.[91] However, published data on which to base the management guidance for transitioning with these agents are limited.[91] In view of this lack of strong evidence, guidance specific to the anticoagulant is provided in the European SmPC (Table 5).[23–25]

In patients taking a direct oral anticoagulant who require transitioning to a parenteral anticoagulant, the direct oral anticoagulant should be discontinued and the first dose of the parenteral anticoagulant should be taken at the time the next dose of direct oral anticoagulant would have been due.[23–25] Conversely, when switching from a parenteral agent to apixaban, the parenteral agent should be discontinued and apixaban administered at the time of the next scheduled dose.[23] When switching from a parenteral agent to rivaroxaban or dabigatran, specific guidance depends on the type of parenteral agent: for a continuously infused parenteral agent (eg, unfractionated heparin), rivaroxaban or dabigatran should be administered at the time of discontinuation;

for a parenteral agent with scheduled administration (eg, low-molecular-weight heparin), rivaroxaban or dabigatran should be given 0–2 hours before the next scheduled dose (Table 5).[24,25]

If transitioning from rivaroxaban or apixaban to warfarin is required in certain clinical circumstances, the Factor Xa inhibitor and warfarin should be given concurrently until the INR is ≥2.0. After 2 days of coadministration, VKA dosing should be guided by INR measurement; INR should be tested just before the next scheduled dose of rivaroxaban or apixaban to minimize its influence on the measured INR. Once the INR is ≥2.0, the Factor Xa inhibitor should be discontinued.[23,25] For patients switching from dabigatran to a VKA, recommendations are based on the patient's renal function; for patients with CrCl ≥50 mL/min, the VKA should be started 3 days before discontinuing dabigatran; for patients with moderate renal impairment (CrCl 30–50 mL/min), the VKA should be started 2 days before the last intake of dabigatran. INR readings should be interpreted with caution until after dabigatran has been stopped for at least 2 days.[71]

Guidance for switching from a VKA to a direct oral anticoagulant is to discontinue the VKA and, depending on the direct oral anticoagulant, initiate treatment when the INR is <2.0 (apixaban and dabigatran) or ≤3.0 (rivaroxaban) (Table 5).[23–25] Physicians should be aware that, in the case of rivaroxaban, recommendations of the target INR level when switching from VKA to rivaroxaban are indication-specific: for patients who are being treated for a VTE and are switching from a VKA to rivaroxaban, the VKA should be stopped and rivaroxaban treatment initiated when the INR is ≤2.5.[25]

Perioperative management

Increasingly, patients with AF taking direct oral anticoagulants may require invasive or surgical intervention. Perioperative management of anticoagulation remains a challenge to physicians, because much consideration must be given to the thromboembolic risk if anticoagulation is interrupted but also to the risk of bleeding in the presence of anticoagulation during or after any invasive procedure. After warfarin therapy is stopped, it takes approximately 4 days for the INR to reach 1.5 (the level at which surgery can safely be performed) in almost all patients.[92] Heparin can be given before the operation to limit the time that the patient remains unprotected.[93] Anticoagulation using warfarin overlapping with a parenteral agent may be resumed 12 hours postoperatively (as long as the patient is not at high risk of postoperative bleeding).[93] Dosing and timing may vary according to whether the patient is at high, medium, or low risk of thrombosis. For patients on direct oral anticoagulants, anticoagulant medication should be discontinued before the procedure and restarted as soon as hemostasis is restored.[23–25]

The EHRA has recently published guidance on the perioperative management of patients on direct oral anticoagulants. For interventions with no clinically important bleeding risk, or where local hemostasis is possible (eg, dental extractions), the procedure may be performed at trough concentrations (ie, 12 hours after last intake of apixaban or dabigatran; 24 hours after last intake of rivaroxaban). For procedures associated with a risk of bleeding, the exact timing of treatment interruption depends on the bleeding risk of the procedure, the renal function of the patient, and the direct oral anticoagulant in use (Table 7).[53]

If a patient requires emergency surgery, anticoagulant medication should be stopped immediately. In an ideal situation, surgery should be deferred until trough plasma levels are reached, although this may be unrealistic, depending on the urgency of the situation. If surgery cannot be delayed, clinicians should evaluate the increased risk of bleeding against the urgency of the intervention. Clinical judgment regarding when the direct oral anticoagulant can be restarted is also important.[23–25]

Table 7 European Heart Rhythm Association recommendations for timing of treatment interruption of approved direct oral anticoagulants prior to elective surgery according to renal function and surgery bleeding risk

Direct oral anticoagulant	Dabigatran		Apixaban or rivaroxaban	
Surgery bleeding risk	**Low[a]**	**High[b]**	**Low[a]**	**High[b]**
Normal renal function (CrCl ≥80 mL/min), hours	≥24	≥48	≥24	≥48
Mild renal impairment (CrCl 50–80 mL/min), hours	≥36	≥72	≥24	≥48
Moderate renal impairment (CrCl 30–50 mL/min), hours	≥48	≥96	≥24	≥48
Severe renal impairment (CrCl 15–30 mL/min), hours	Dabigatran contraindicated		≥36	≥48
Renal failure (CrCl <15 mL/min)	Dabigatran contraindicated		Apixaban and rivaroxaban not recommended	

Notes: [a]Surgeries/procedures with low risk of bleeding include: endoscopy with biopsy, prostate or bladder biopsy, electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia, angiography, and pacemaker or implantable cardioverter defibrillator implantation; [b]surgeries/procedures with high risk of bleeding include: complex left-sided ablation, spinal or epidural anesthesia, lumbar diagnostic puncture, thoracic surgery, abdominal surgery, major orthopedic surgery, liver biopsy, transurethral prostate resection, and kidney biopsy. Adapted from Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013, 15, 5, 625–651, by permission of Oxford University Press.[53]
Abbreviation: CrCl, creatinine clearance.

Conclusion

Direct oral anticoagulants have been demonstrated in Phase III clinical trials to be noninferior to warfarin in preventing stroke and systemic embolism in nonvalvular AF, with a favorable benefit–risk profile. Indeed, the incidence of ICH and fatal bleeding is significantly lower compared with warfarin. ESC guidelines now recommend direct oral anticoagulants over VKAs for most patients with nonvalvular AF.[8]

The ability of the direct oral anticoagulants to target one specific component in the coagulation cascade, together with their fast onset of action, short half-lives, and low potential for food or drug interactions, differentiates them from the VKAs. These qualities enable direct oral anticoagulants to be administered in fixed doses without routine coagulation monitoring.

Specific care protocols for individual patients will further allow physicians to maximize the efficacy of antithrombotic therapy of their patients and reduce the risk of bleeding complications when using direct oral anticoagulants.

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