Evolving Treatments for Arterial and Venous Thrombosis
Role of the Direct Oral Anticoagulants

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Abstract: **The direct oral anticoagulants (DOACs) represent a major advance in oral anticoagulant therapy and have replaced the vitamin K antagonists as the preferred treatment for many indications. By simplifying long-term anticoagulant therapy and improving its safety, the DOACs have the potential to reduce the global burden of thrombosis. Postmarketing studies suggest that the favorable results achieved with DOACs in the randomized controlled trials can be readily translated into practice, but highlight the need for appropriate patient, drug and dose selection, and careful follow-up. Leveraging on their success to date, ongoing studies are assessing the utility of DOACs for the prevention of thrombosis in patients with embolic stroke of unknown source, heart failure, coronary artery disease, peripheral artery disease, antiphospholipid syndrome, and cancer. The purpose of this article is to (1) review the pharmacology of the DOACs, (2) describe the advantages of the DOACs over vitamin K antagonists, (3) summarize the experience with the DOACs in established indications, (4) highlight current challenges and limitations, (5) highlight potential new indications; and (6) identify future directions for anticoagulant therapy. (*Circ Res*. 2016;118:1409-1424. DOI: 10.1161/CIRCRESAHA.116.306925.)**

Key Words: anticoagulants ■ atrial fibrillation ■ cardiovascular disease ■ thromboembolism ■ warfarin

Thromboembolism involving the arterial or venous circulation is the most common cause of morbidity and mortality worldwide.[1] Anticoagulation therapy is a cornerstone of thromboembolism prevention and treatment. Vitamin K antagonists (VKAs) such as warfarin were the only orally administered anticoagulants for >60 years. Although VKAs are effective, they have numerous limitations. Thus, VKAs produce a variable anticoagulant response that is influenced by numerous drug–drug and drug–food interactions and by common genetic polymorphisms that affect their pharmacokinetic and pharmacodynamic properties. Consequently, the dose varies from patient to patient, and routine coagulation monitoring is essential to ensure that a therapeutic anticoagulant effect is obtained. The multiple limitations of VKAs prompted a search for new oral anticoagulants that could be administered in fixed doses without the need for coagulation monitoring.

Elucidation of the crystal structures of thrombin and factor Xa (FXa) enabled structure-based design of small molecules that bind to the active site of these enzymes with high affinity and specificity.[2,3] Ximelagatran, a reversible inhibitor of thrombin, was the first direct oral anticoagulant (DOAC) licensed for clinical use.[4,5] Although withdrawn

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Nonstandard Abbreviations and Acronyms	
AF	atrial fibrillation
CI	confidence interval
DOAC	direct oral anticoagulant
HR	hazard ratio
INR	international normalized ratio
LMWH	low-molecular-weight heparin
VTE	venous thromboembolism

from the market soon thereafter because of potential hepatotoxicity, the clinical trial program that led to its approval set the stage for the design and development of the currently approved DOACs.[6]

Four DOACs are now licensed: dabigatran, which inhibits thrombin[7]; and rivaroxaban,[8] apixaban, and edoxaban,[9,10] which inhibit factor Xa. In phase 3 randomized clinical trials that included >100 000 patients, these agents have proven to be at least as effective as VKAs and to produce less bleeding, particularly less intracranial bleeding.[11] Importantly, the DOACs are more convenient to administer than VKAs because they have a rapid onset and offset of action, which facilitates their initiation and periprocedural management and because they can be given in fixed doses without routine laboratory monitoring. By simplifying long-term anticoagulant therapy and improving its safety, the DOACs have the potential to reduce the global burden of thrombosis. Licensed for stroke prevention in atrial fibrillation (AF) and for the prevention and treatment of venous thromboembolism (VTE), ongoing trials are investigating the utility of the DOACs in other disorders. The purpose of this article is to (1) review the pharmacology of the DOACs, (2) describe the advantages and potential disadvantages of the DOACs compared with VKAs, (3) summarize the experience with the DOACs in established indications, (4) highlight current challenges and limitations, (5) outline potential new indications, and (5) identify future directions for anticoagulant therapy.

Pharmacology of DOACs

The pharmacological properties of the DOACs are summarized in Table 1. DOACs are small molecules that bind to the active site of their target enzyme in a reversible fashion.[7–10] Dabigatran etexilate is a prodrug that requires metabolic activation by esterases to transform it into dabigatran.[12] In contrast, rivaroxaban, apixaban, and edoxaban are active drugs.[13–15] Whereas the oral bioavailability of dabigatran is ≈6%, the bioavailability of rivaroxaban, apixaban, and edoxaban exceeds 50%.[12–15] When given in treatment doses, the absorption of rivaroxaban is increased by food.[16] In contrast, food has little on the absorption of the other DOACs.[17–19]

The DOACs have a rapid onset of action with peak concentrations achieved in 1 to 4 hours. Although the half-lives vary, they all are ≈12 hours. Rivaroxaban and apixaban are metabolized via the cytochrome P450 system, particularly CYP3A4, whereas edoxaban and dabigatran undergo little cytochrome P450–mediated metabolism.[12–15] Therefore, the concentrations of rivaroxaban and apixaban can be increased or decreased by potent inhibitors or inducers of CYP3A4, respectively.[20,21] All of the DOACs are substrates for P-glycoprotein and potent inhibitors or inducers of P-glycoprotein can increase or decrease the plasma concentrations of the DOACs, respectively.[22–25] The DOACs are cleared through renal and extrarenal pathways. The extent of renal clearance varies and of the absorbed unchanged drug, the kidneys are responsible for clearance of 80% of dabigatran, 50% of edoxaban, 33% of rivaroxaban, and 27% of apixaban.[12–15] Consequently, the DOACs can accumulate in patients with severe renal impairment, they should not be used in patients with a creatinine clearance <15 mL/min, and they should be used with caution in those with a creatinine clearance between 15 and 30 mL/min.[26–29]

Table 1. Comparative Pharmacology of Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability, %	6–7	66	50	62
Protein binding, %	35	92–95	87	40–59
Time to Cmax, h	2	2–4	1–3	1–2
Half-life, h	12–14	9–13	8–15	9–14
Efflux transporters	P-gp	P-gp/BCRP	P-gp	P-gp
Metabolism via CYP450, %	<2	57	<32	<5
Renal elimination,* %	>80†	33‡	25‡	50‡
Drug interactions	P-gp inhibitors and inducers	Dual inhibitors and inducers of CYP3A4 and P-gp	Dual inhibitors and inducers of CYP3A4 and P-gp	P-gp inhibitors and inducers

BCRP indicates breast cancer resistance protein; CYP450, cytochrome P450; and P-gp, p-glycoprotein.

*Proportion of drug excreted unchanged in urine.

†Intravenous dose.

‡Oral absorbed drug.

The distinct pharmacological properties of the DOACs endow them with potential advantages and disadvantages compared with VKAs. These are summarized in the following section.

Advantages and Disadvantages of DOACs Compared With VKAs

The advantages of the DOACs over VKAs are summarized in Table 2. First, the DOACs have a more rapid onset of action than VKAs, which obviates the need for bridging with a parenteral anticoagulant in most situations.[30,31] Second, the short half-lives of the DOACs streamline periprocedural management and reduce the need for reversal agents. Third, in contrast to VKAs, the anticoagulant effect of the DOACs is not influenced by dietary vitamin K and there are few drug–drug interactions. Consequently the DOACs produce a more

Table 2. Potential Advantages and Disadvantages of DOACs Over Vitamin K Antagonist

	Implications
Advantages	
Decreased risk of intracranial bleeding	Safer anticoagulant therapy
Predictable anticoagulant effect	Convenience of fixed dosing without routine laboratory monitoring
Quick onset of action	Obviates need for heparin/low molecular weight heparin bridging
Quick offset of action	Simplifies periprocedural management and reduces need for reversal agents
Fewer drug and food interactions	Predictable anticoagulant effect
Disadvantages	
Higher acquisition cost	Limits uptake in some countries and patient groups
Reversal agents for oral factor Xa inhibitors not yet licensed	Limits uptake because of perceived concern about uncontrollable bleeding Complicates management of patients who require urgent intervention
Limited access to standardized assays for drug level measurement	Complicates identification of bleeding patients who require reversal and timing of urgent surgery or intervention
Dependence on renal clearance	Contraindicates use of DOACs in patients with severe renal failure
Fecal excretion of active anticoagulant	May predispose at-risk patients to gastrointestinal bleeding

DOAC indicates direct oral anticoagulants.

predictable anticoagulant response, which enables administration in fixed doses without routine coagulation monitoring. Finally, the DOACs produce less intracranial bleeding than VKAs.[32]

Despite the many advantages, the DOACs also have limitations (Table 2). Whereas VKAs are administered once daily, some of the DOACs require twice daily dosing, at least for some indications. VKAs are not cleared by the kidneys. In contrast, because the DOACs are cleared, at least in part, by the kidneys, they can accumulate in patients with renal impairment. Consequently, renal function must be monitored in patients given DOACs, whereas this is less important with VKAs. The anticoagulant effect of VKAs is monitored using the international normalized ratio (INR), which is standardized worldwide.[33] In contrast, DOACs have variable and reagent-dependent effects on global tests of coagulation, such as the activated partial thromboplastin time or prothrombin time.[34] Although plasma concentrations of dabigatran can be quantified using a diluted thrombin time or ecarin clotting time and those of rivaroxaban, apixaban, and edoxaban can be determined using a chromogenic anti-FXa assay, not only must these tests be properly calibrated but also they are not widely available and even when available, the turnaround time can be long.[35] The lack of assays to measure the anticoagulant effect or plasma levels of the DOACs can be problematic in patients who present with serious bleeding or in those requiring urgent surgery or intervention. Likewise, without such assays, important drug–drug interactions cannot be identified. Finally, VKAs can be reversed with vitamin K and prothrombin complex concentrate. Although idarucizumab is available to reverse dabigatran, reversal agents for rivaroxaban, apixaban, and edoxaban are not yet licensed.[36–38]

Licensed Indications for the DOACs

DOACs are licensed for stroke prevention in AF, treatment of VTE, which includes deep vein thrombosis and pulmonary embolism, and for postoperative thromboprophylaxis in patients undergoing elective hip or knee arthroplasty. In some jurisdictions, rivaroxaban is also licensed for prevention of recurrent ischemia in stabilized patients with acute coronary syndrome (Table 3).

Stroke Prevention in AF

AF is the most common sustained cardiac arrhythmia and is responsible for ≈20% of ischemic strokes.[39] Patients with AF have an annual risk of stroke of ≈5%, which can be reduced by two thirds with VKAs.[40] Despite their proven efficacy, however, VKAs are used in only ≈50% of eligible AF patients and even when used, the INR is frequently below or above the therapeutic range, which can predispose patients to ischemic stroke or serious bleeding, respectively.[41,42] Therefore, AF is a major cause of morbidity and mortality.

Dabigatran, rivaroxaban, apixaban, and edoxaban were compared with warfarin for stroke prevention in 4 randomized trials that included 71 683 patients with nonvalvular AF.[43–46] In addition, apixaban was compared with aspirin in AF patients who were unable or unwilling to take VKAs.[47] Universal criteria for defining nonvalvular AF are lacking,[48–50] and definitions varied across the trials.[51] In general, patients with AF in association with moderate-to-severe mitral stenosis or mechanical heart valves are considered to have valvular AF and were uniformly excluded from the phase 3 trials.[51]

As a class, the higher doses of the DOACs reduced the risk of stroke or systemic embolism by 19% compared with warfarin (relative risk [RR], 0.81; 95% confidence interval [CI], 0.73–0.91).[52] This reduction was largely driven by a 51% decrease in the rate of hemorrhagic stroke (RR, 0.49; 95% CI, 0.38–0.64). Compared with warfarin, DOACs were associated with a 52% decrease in the risk of intracranial bleeding (RR, 0.48; 95% CI, 0.39–0.59), but an increased risk of gastrointestinal bleeding (RR, 1.25; 95% CI, 1.01–1.55). Overall, the rate of major bleeding with the DOACs was similar to that with warfarin (RR, 0.86; 95% CI, 0.73–1.00). Compared with warfarin, the lower doses of the DOACs reduced the risk of stroke and systemic embolism to a similar extent (RR, 1.03; 95% CI, 0.84–1.27), but were associated with less major bleeding (RR, 0.65; 95% CI, 0.43–1.00), and more ischemic stroke (RR, 1.28; 95% CI, 1.02–1.60).

When compared with aspirin in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study, apixaban reduced

Table 3. Licensed Indications and Dosing Recommendations

Licensed Indications	Dabigatran Etexilate		
	US	EU	Canada
Stroke prevention in atrial fibrillation			
Phase III trials	RE-LY		
Approved full doses	150 mg BID	150 mg BID	150 mg BID
Dose adjustments	75 mg BID if CrCl 15–30 mL/min or CrCl 30–50 mL/min with concomitant dronedarone or ketoconazole	110 mg BID if age ≥80 y or concomitant verapamil or if high bleeding risk: age 75–80 y or moderate renal impairment or predisposition to GI bleeding	110 mg BID if Age ≥80 y or age >75 y with 1 risk factor for bleeding (moderate renal impairment, P-gp inhibitor, NSAID, antiplatelet agent, or predispositions to GI bleeding)
Acute VTE treatment			
Phase III trials	RE-COVER		
	RE-COVER II		
Approved full doses	150 mg BID after LMWH	150 mg BID after LMWH	150 mg BID after LMWH
Dose adjustments	N/A	110 mg BID if age ≥80 y or concomitant verapamil or if high bleeding risk: age 75–80 y or moderate renal impairment or predisposition to GI bleeding	110 mg BID if Age ≥80 y or age >75 y with 1 risk factor for bleeding (moderate renal impairment, P-gp inhibitor, NSAID, antiplatelet agent, or predispositions to GI bleeding)
Secondary VTE prevention			
Phase III trials	RE-MEDY		
	RE-SONATE		
Approved full doses	150 mg BID after LMWH	150 mg BID after LMWH	150 mg BID after LMWH
Dose adjustments	Similar to acute VTE treatment		
VTE prevention in major orthopaedic surgery			
Phase III trials	RE-MOBILIZE, RE-MODEL, RE-NOVATE, RE-NOVATE-II		
Approved full doses	110 mg first dose, followed by 220 mg OD following hip replacement surgery only CrCl >30 mL/min	110 mg first dose, followed by 220 mg OD	110 mg first dose, followed by 220 mg OD
Dose adjustments	N/A	75 mg first dose followed by 150 mg OD if any of the following: CrCl 30–50 m/min, concomitant use of P-glycoprotein inhibitor, age ≥75 y	75 mg first dose followed by 150 mg OD if any of the following: CrCl 30–50 m/min, concomitant use of P-gp inhibitor, age ≥75 y or 75 mg daily if CrCl 30–50 mL/min and taking P-gp inhibitor
Acute coronary syndrome			
Not approved			

(*Continued*)

ADVANCE indicates Apixaban Dose Orally vs. Anticoagulation with Enoxaparin; AMPLIFY, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; AMPLIFY-EXT, Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CrCl, creatinine clearance; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis Without Symptomatic Pulmonary Embolism; EINSTEIN-EXT, Once-Daily Oral Rivaroxaban Versus Placebo in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism; EINSTEIN PE, Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism; ENGAGE-AF, The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; EU, Europe; GI, gastrointestinal; HOKUSAI-VTE, Edoxaban Versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism; LMWH, low-molecular-weight heparin; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drugs; P-gp, P-glycoprotein; RE-COVER, Efficacy and Safety of Dabigatran Compared to Warfarin for 6-Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate; RE-MEDY, Dabigatran or Warfarin for Extended Maintenance Therapy of Venous Thromboembolism; RE-MOBILIZE, Oral Thrombin Inhibitor Dabigatran Etexilate Versus North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty; RE-MODEL, Oral Dabigatran Etexilate vs. Subcutaneous Enoxaparin for the Prevention of Venous Thromboembolism After Total Knee Replacement; RE-NOVATE, RE-NOVATE-II, Oral Dabigatran Versus Enoxaparin for Thromboprophylaxis After Primary Total Hip Arthroplasty; RE-SONATE, Twice-Daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; RECORD, Rivaroxaban Versus Enoxaparin for Thromboprophylaxis After Total Knee Arthroplasty; ROCKET-AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation; STARS, Studying Thrombosis After Replacement Surgery; US, United States; and VTE, venous thromboembolism.

Table 3. Continued

Rivaroxaban			Apixaban			Edoxaban	
US	EU	Canada	US	EU	Canada	US	EU
ROCKET-AF			ARISTOTLE, AVERROES			ENGAGE-AF	
20 mg OD with evening meal	20 mg OD with food	20 mg OD with food	5 mg BID	5 mg BID	5 mg BID	60 mg OD if CrCl >50 to ≤95 mL/min	60 mg OD
15 mg OD if CrCl 15–50 mL/min	15 mg OD if CrCl 15–49 mL/min	15 mg OD if CrCl 30–49 mL/min	2.5 mg BID if at least 2 of the following: age ≥80 y, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL			30 mg OD if CrCl 15 to 50 mL/min	30 mg OD if one or more of the following: CrCl 15–50 mL/min, weight ≤60 kg or concomitant use of potent P-gp inhibitor
EINSTEIN DVT EINSTEIN PE			AMPLIFY			HOKUSAI-VTE	
15 mg BID for 3 wk followed by 20 mg OD	15 mg BID for 3 wk followed by 20 mg OD	15 mg BID for 3 wk followed by 20 mg OD	10 mg BID for 7 d, followed by 5 mg BID	10 mg BID for 7 d, followed by 5 mg BID	10 mg BID for 7 d, followed by 5 mg BID	60 mg OD after LMWH	60 mg OD after LMWH
N/A	N/A	N/A	N/A	N/A	N/A	30 mg OD if ≥1 of the following: CrCl 15–50 mL/min, weight ≤60 kg or concomitant use of potent P-gp inhibitor	
EINSTEIN-EXT			AMPLIFY-EXT			HOKUSAI-VTE	
20 mg OD	20 mg OD	20 mg OD	2.5 mg BID	2.5 mg BID	2.5 mg BID	Not approved	60 mg OD
N/A	N/A	N/A	N/A	N/A	N/A	Not approved	Similar to acute VTE treatment
RECORD 1 to 4			ADVANCE 1 to 3			STARS J-5	
10 mg OD	10 mg OD	10 mg OD	2.5 mg BID	2.5 mg BID	2.5 mg BID	Not approved	Not approved
N/A							
Not approved	2.5 mg BID	Not approved	Not approved			Not approved	

the risk of stroke and systemic embolism by 55% (hazard ratio [HR], 0.45; 95% CI, 0.32–0.62) and was associated with a similar rate of major bleeding (HR, 1.13; 95% CI, 0.74–1.75).[47] Therefore, the results of this trial highlight the limitations of aspirin for stroke prevention in AF patients and indicate that the DOACs are a better choice.

With the efficacy and safety of the DOACs established for stroke prevention in patients with nonvalvular AF and with the convenience of fixed dosing without the need for routine coagulation monitoring, most clinical guidelines now give preference to the DOACs over VKAs for stroke prevention in most AF patients.[49,50,53] However, DOACs are contraindicated in patients with moderate-to-severe mitral stenosis or mechanical heart valves.[48–50] The DOACs can be used in patients with nonrheumatic valve disease because many such patients were included in the phase 3 trials.[51] Based on expert consensus, it is also reasonable to consider DOACs in patients with bioprosthetic heart valve and in those who have undergone mitral valve repair.[51] It may be prudent to avoid DOACs in patients with newly implanted bioprosthetic valves because they may not prevent thrombosis on the sewing ring. The sewing ring endothelializes within 3 months of implantation, and the DOACs are a reasonable option at this point.

Because of their ease of use, reviews of prescription databases and registries have shown progressive uptake of the DOACs in place of VKAs.[54–57] However, there continues to be a proportion of AF patients who are not receiving any antithrombotic therapy or are receiving aspirin in place of an anticoagulant.[58] Therefore, the gap in translating knowledge into practice remains.

DOACs for Treatment of VTE

Conventional treatment of VTE starts with a rapidly acting parenteral anticoagulant, usually subcutaneous low-molecular-weight heparin (LMWH), which is overlapped with a VKA. The LMWH is given for ≥5 days and is stopped when the INR is therapeutic. Patients are then maintained on a VKA for ≥3 months at which point the risk of recurrent VTE if anticoagulation is stopped is balanced with the risk of bleeding with continued treatment. A 3-month course of anticoagulation therapy is adequate for most patients whose VTE was provoked by well-recognized but transient risk factors such as major surgery. In contrast, patients with unprovoked VTE are often maintained on extended anticoagulation therapy.

The DOACs were compared with conventional anticoagulation therapy in 27 023 patients with acute VTE in 6 phase 3 randomized trials: Efficacy and Safety of Dabigatran Compared to Warfarin for 6-Month Treatment of Acute Symptomatic Venous Thromboembolism (RECOVER) I and II with dabigatran,[59,60] Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis Without Symptomatic Pulmonary Embolism (EINSTEIN DVT) and Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism (EINSTEIN-PE) with rivaroxaban,[61,62] Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) with apixaban,[63] and Edoxaban Versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism (HOKUSAI VTE) with edoxaban.[64] The primary efficacy end point in these trials was recurrent VTE or VTE-related death, whereas the primary safety outcome was either major bleeding or the composite of major and clinically relevant nonmajor bleeding. In a pooled analysis of the 6 trials, recurrent VTE and VTE-related deaths occurred in 2.0% of DOAC recipients compared with 2.2% of those given a VKA (relative risk [RR], 0.90; 95% CI, 0.77–1.06).[65] Compared with VKAs, DOACs were associated with a 39% reduction in the risk of major bleeding (RR, 0.61; 95% CI, 0.45–0.83), a 63% reduction in intracranial bleeding (RR, 0.37; 95% CI, 0.21–0.68), and a 64% reduction in fatal bleeding (RR, 0.36; 95% CI, 0.15–0.84). In addition, clinically relevant nonmajor bleeding was reduced by 27% with the DOACs compared with VKAs (RR, 0.73; 95% CI, 0.58–0.93). Therefore, the DOACs are noninferior to well-managed VKA therapy, but are associated with significantly less bleeding.[65]

Whereas dabigatran and edoxaban were started after a minimum of a 5-day course of parenteral anticoagulant therapy, rivaroxaban and apixaban were administered in all-oral regimens starting with a higher dose for 21 and 7 days, respectively. When used in this all-oral fashion, both agents were noninferior to conventional therapy and were associated with significantly less major bleeding. Therefore, the DOACs simplify VTE treatment and facilitate out-of-hospital management of most patients with deep vein thrombosis and many with pulmonary embolism, thereby reducing healthcare costs. With these advantages, the most recent clinical guidelines now endorse DOACs as first-line VTE treatment.[66]

VTE patients requiring thrombolytic therapy for massive pulmonary embolism or extensive deep vein thrombosis are usually treated with unfractionated heparin to start, but can be switched to a DOAC when their condition stabilizes. The DOACs are contraindicated in pregnancy because they cross the placenta and they should not be used in nursing mothers because it is uncertain whether they pass into the breast milk.[67] VKAs remain the treatment of choice for pulmonary embolism patients with severe renal impairment (creatinine clearance <15 mL/min) and for those with antiphospholipid syndrome, particularly when it is associated with arterial thrombosis. Although the data with DOACs in patients with cancer-associated VTE are promising,[65] few such patients were included in the randomized trials. Consequently, guidelines continue to recommend LMWH as first-line therapy in patients with cancer-associated thrombosis.[68] However, ongoing trials are comparing DOACs with LMWH in such patients (Table 4).

Rivaroxaban, apixaban, and dabigatran have been compared with placebo for secondary VTE prevention in patients who received ≥6 months of anticoagulation therapy for their index event in the Once-Daily Oral Rivaroxaban Versus Placebo in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN-Extension),[61] Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment (AMPLIFY-EXT), and Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE (RE-SONATE) trials,[69,70] respectively, and dabigatran was compared with warfarin for extended therapy

Table 4. Ongoing Direct Oral Anticoagulants Trials in New Indications

Indications	Trial/NCT no	Intervention	Control	Duration	Efficacy outcome	Safety outcome	Patient No.
CAD/PAD	COMPASS NCT01776424	Rivaroxaban 2.5 mg BID+aspirin 100 mg or rivaroxaban 5 mg BID+ placebo	Aspirin+placebo	5 y	MACE	Major bleeding	27 400
PAD undergoing revascularization	VOYAGER-PAD NCT02504216	Rivaroxaban 2.5 mg BID	Placebo	2 y	MACE	Major bleeding	6500
ESUS	RE-SPECT ESUS NCT02239120	Dabigatran 110 or 150 mg BID	Aspirin	36 mo	Stroke	Major bleeding	6000
ESUS	NAVIGATE ESUS NCT02313909	Rivaroxaban 15 mg OD	Aspirin	3 y	Stroke or SEE	Major bleeding	7060
ESUS	ATTICUS NCT02427126	Apixaban 5 mg BID	Aspirin	12 mo	MRI ischemic lesion	NR	500
ACS	GEMINI ACS 1 NCT02293395	Rivaroxaban 2.5 mg BID+ticagrelor or clopidogrel	Aspirin+ticagrelor or clopidogrel	180 d	NR	Clinically significant bleeding	3000
AF+ACS undergoing PCI	RE-DUAL-PCI NCT01264864	Dabigatran 110 mg BID+P2Y12 inhibitor	Warfarin+P2Y12 inhibitor+aspirin	30 mo	MACE	Major bleeding	2500
AF+ACS undergoing PCI	PIONEER AF PCI NCT01830543	Rivaroxaban 2.5 mg BID+DAPT, rivaroxaban 15 mg OD+P2Y12 inhibitor	VKA+DAPT	12 mo	MACE	Clinically relevant bleeding	2127
AF+ACS undergoing PCI	Apixaban in ACS NCT02415400	Apixaban 5 or 2.5 mg BID	VKA	6 mo	MACE	Clinically relevant bleeding	4600
Post-surgical MI	MANAGE NCT01661101	Dabigatran 110 mg BID and omeprazole 20 mg OD	Placebo	12 mo	MACE	Major bleeding	3200
Post-hospital discharge VTE prevention in medically ill	MARINER NCT02111564	Rivaroxaban 10 or 7.5 mg OD	Placebo	45 d	VTE+VTE-related death	Major bleeding	8000
VTE prevention in medically ill	APEX NCT01583218	Betrixaban 80 mg OD for 35 d+placebo	Enoxaparin 40 mg SC OD for 10 d+placebo	35 d	VTE+VTE-related death	Major bleeding	7500
VTE prevention in nonmajor orthopaedic surgery	PRONOMOS NCT02401594	Rivaroxaban 10 mg OD (≤3 mo)	Enoxaparin 4000 IU OD (≤3 mo)	3 mo	VTE	Major bleeding	4400
Cancer VTE prevention	AVERT NCT02048865	Apixaban 2.5 mg BID	Placebo	6 mo	VTE	Clinically relevant bleeding	574
Cancer VTE prevention	Apixaban VTE Prevention Following Gynecologic Cancer Surgery. NCT02366871	Apixaban 2.5 mg BID for 28 d after surgery	Enoxaparin 40 mg OD for 28 d after surgery	28 d	VTE	Major bleeding	400
Secondary VTE prevention	EINSTEIN CHOICE NCT02064439	Rivaroxaban 10 or 20 mg OD	Aspirin	12 mo	VTE	Major bleeding	2850
Cancer VTE treatment	HOKUSAI Cancer VTE NCT02073682	Edoxaban 60 or 30 mg OD	Dalteparin	6 mo	VTE	Clinically relevant bleeding	1000
Cancer VTE treatment	Apixaban in cancer VTE treatment. NCT02585713	Apixaban BID	Enoxaparin	180 d	VTE	Major bleeding	315
Low-risk AF and cognitive decline	BRAIN-AF NCT02387229	Rivaroxaban 15 mg OD	Aspirin	78 mo	Stroke+TIA+ neurocognitive decline	Major clinical bleeding	6396
Heart Failure	COMMANDER HF NCT01877915	Rivaroxaban 2.5 mg BID	Placebo	30 mo	MACE	Major bleeding	5000
Device-detected subclinical AF	ATRESiA NCT01938248	Apixaban 5 or 2.5 mg BID	Aspirin	3 y	Stroke+SEE	Major bleeding	4000

(*Continued*)

Table 4. Continued

Indications	Trial/NCT no	Intervention	Control	Duration	Efficacy outcome	Safety outcome	Patient No.
TAVR	GALILEO NCT02556203	Rivaroxaban 10 mg+ aspirin 100 mg	Aspirin+clopidogrel for first 90 d	25 mo	MACE	Clinically relevant bleeding	1520
TAVR	ATLANTIS NCT02664649	Apixaban 5 or 2.5 mg BID	VKA or antiplatelet	13 mo	MACE	Major bleeding	1509
AF cardioversion	ENSURE-AF NCT02072434	Edoxaban 60 or 30 mg OD (28–49 d)	Enoxaparin/VKA for 28–49 d	≤49 d	MACE	Clinically relevant bleeding	2199
AF cardioversion	EMANATE NCT01200228	Apixaban 2.5 or 5 mg BID	Heparin/VKA	1 mo	Stroke+systemic embolism	Major bleeding	1500
Pulmonary Vein ablation	RE-CIRCUIT NCT02348723	Dabigatran 150 mg BID	Warfarin	2 mo	MACE	Major bleeding	724
Pulmonary vein ablation	ODIn-AF NCT02067182	Dabigatran 150 or 110 mg BID ongoing	Dabigatran 110 or 150 mg BID for 3 mo	12 mo	MRI ischemic lesion	Any bleeding	630
Catheter ablation	OCEAN NCT02168829	Rivaroxaban 20 mg OD	Aspirin	3 y	Stroke+SEE+silent infarction	Major and minor bleeding	1452
Catheter ablation	AEIOU NCT02608099	Uninterrupted apixaban	Interrupted apixaban	1 mo	Stroke+SEE	Major bleeding	360
Catheter ablation	AXAFA NCT02227550	Apixaban 5 mg BID	VKA INR target 2–3	≥30 d	MACE	Any bleeding	650
Antiphospholipid syndrome	TRAPS NCT02157272	Rivaroxaban 20 mg OD	Warfarin	4 y	Thrombosis	Bleeding	536
Antiphospholipid syndrome	ASTRO-APS NCT02295475	Apixaban 5 mg BID	Warfarin INR target 2–3	13 mo	Arterial and venous thrombosis	Clinically relevant bleeding	200
Superficial thrombophlebitis	RASET NCT02123524	Rivaroxaban 10 mg OD	Placebo	45 d	VTE	Major bleeding	600
Prevention of paradoxical emboli in PFO and endocardial device leads	PARADOX NCT02378623	Apixaban 5 or 2.5 mg BID	Placebo	2 y	MRI ischemic lesion	NR	400

ACS indicates acute coronary syndrome; AEIOU, Apixaban Evaluation of Interrupted Or Uninterrupted Anticoagulation for Ablation of Atrial Fibrillation; AF, atrial fibrillation; APEX, Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study; ASTRO-APS, Apixaban for the Secondary Prevention of Thromboembolism Among Patients With the AntiphosPholipid Syndrome; ATLANTIS, Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; ATRESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; ATTICUS, Apixaban for Treatment of Embolic Stroke of Undetermined Source; AVERT, Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients; AXAFA, Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy; BRAIN-AF, Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; CAD, coronary artery disease; COMMANDER HF, A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure; COMPASS, Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; DAPT, dual antiplatelet therapy; EINSTEIN CHOICE, Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism; EMANATE, Study Of The Blood Thinner, Apixaban, For Patients Who Have An Abnormal Heart Rhythm (Atrial Fibrillation) And Expected To Have Treatment To Put Them Back Into A Normal Heart Rhythm (Cardioversion); ENSURE-AF, Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation; ESUS, embolic stroke of unknown source; GALILEO, Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes; GEMINI, A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome; HOKUSAI, Edoxaban Versus Warfarin for the Treatment of Symptomatic; INR, international normalized ratio; MACE, major adverse cardiovascular events; MANAGE, Management of Myocardial Injury After Noncardiac Surgery Trial; MARINER, A Study of Rivaroxaban (JNJ39039039) on the Venous Thromboembolic Risk in Posthospital Discharge Patients; MI, myocardial infarction; MRI, magnetic resonance imaging; NAVIGATE, Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS); NR, not reported; OCEAN, Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial; ODIn-AF, Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation With Dabigatran After Pulmonary Vein Isolation for Atrial Fibrillation; P2Y12, purinergic receptor P2Y12; PAD, peripheral artery disease; PARADOX, Patients With Patent Foramen Ovale and Endocardial Device Leads on Apixaban for Prevention of Paradoxical Emboli; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; PIONEER AF, A Study Exploring Two Strategies of Rivaroxaban (JNJ39039039; BAY-59-7939) and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; PRONOMOS, PROphylaxis in NOn Major Orthopaedic Surgery; RASET, Rivaroxaban Anticoagulation for Superficial Vein Thrombosis; RE-CIRCUIT, Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation; RE-DUAL-PCI, Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; RE-SPECT ESUS, Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source; SEE, systemic embolic event; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; TRAPS, Rivaroxaban in Thrombotic Antiphospholipid Syndrome; VKA, vitamin K antagonists; VOYAGER-PAD, Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities; and VTE, venous thromboembolism.

in the Dabigatran or Warfarin for Extended Maintenance Therapy of Venous Thromboembolism (RE-MEDY) trial.[70] Pooled analyses of the 3 placebo-controlled trials revealed a significant reduction in the rate of recurrent VTE and VTE-related mortality with the DOACs compared with placebo, but an increased rate of major and clinically relevant nonmajor bleeding.[71,72] In contrast to the other 2 trials, the AMPLIFY-EXT trial compared 2 dosing regimens of apixaban (2.5 and 5 mg BID) with placebo to identify the dose providing the best balance of efficacy and safety.[69] The risk of recurrent VTE with the lower dose apixaban regimen was similar to that with the higher dose regimen (RR, 0.97; 95% CI, 0.46–2.02) and neither regimen was associated with a significant increase in major bleeding compared with placebo, but there was a trend for less clinically relevant bleeding with the lower dose regimen than with the higher dose regimen (RR, 0.74; 95% CI, 0.46–1.22). These findings suggest a superior benefit-to-risk profile with the lower dose apixaban regimen than with the higher dose regimen. This is not the case with warfarin. Thus, the rate of recurrent VTE was higher with lower-intensity warfarin (target INR of 1.5–2) than with usual-intensity warfarin (target INR of 2–3) in The Extended Low-Intensity Anticoagulation for Thrombo-Embolism (ELATE) trial,[73] whereas rates of major bleeding were similar. Because the risk of bleeding is often the limiting factor in the decision to extend the duration of anticoagulation therapy, the results with low-dose apixaban may prompt more clinicians to prescribe extended VTE treatment. The ongoing Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) trial is comparing 2 dosing regimens of rivaroxaban (10 and 20 mg OD) with aspirin to identify the optimal dose of rivaroxaban for extended VTE treatment and to determine whether rivaroxaban is superior to aspirin for this purpose.[74]

In the RE-MEDY study, dabigatran was noninferior to warfarin (HR, 1.44; 95% CI, 0.78–2.64), but was associated with a 46% reduction in the composite of major or clinically relevant nonmajor bleeding (HR, 0.54; 95% CI, 0.41–0.71).[70] Therefore, the DOACs are an effective, safe, and convenient option for both the initial and the extended treatment of VTE.

DOACs for VTE Prevention

Without thromboprophylaxis, patients undergoing elective hip or knee arthroplasty are at risk for VTE and this risk persists for several weeks after the surgery. Traditionally, LMWH was used for prophylaxis, but with hospital stays progressively shortening, the burden of prophylaxis persists after hospital discharge and the need for daily subcutaneous injections is burdensome for many patients. Consequently, the DOACs offer an attractive alternative to LMWH for postoperative thromboprophylaxis in orthopedic patients.

Dabigatran,[75–78] rivaroxaban,[79–82] apixaban,[83–85] and edoxaban[86,87] were compared with enoxaparin in patients undergoing hip or knee arthroplasty. The phase 3 trials with edoxaban were conducted in Japan where the prophylactic dose of enoxaparin is lower than that in other countries.[86,87] Consequently, edoxaban is licensed in Japan for this indication but not in other countries. In a pooled analysis of the trials with the other DOACs, rivaroxaban reduced the risk of symptomatic VTE compared with enoxaparin (RR, 0.48; 95% CI, 0.31–0.75), whereas the risk of symptomatic VTE with dabigatran was similar to that with enoxaparin (RR, 0.71; 95% CI, 0.23–2.12) as it was with apixaban (RR, 0.82; 95% CI, 0.41–1.64).[88] The risk of clinically relevant bleeding was higher with rivaroxaban than with enoxaparin (RR, 1.25; 95% CI, 1.05–1.49). In contrast, dabigatran was associated with a similar rate of clinically relevant bleeding compared with enoxaparin (RR, 1.12; 95% CI, 0.94–1.35), whereas apixaban was associated with a lower risk (RR, 0.82; 95% CI, 0.69–0.98). Therefore, the DOACs streamline thromboprophylaxis after elective hip or knee arthroplasty, and they are generally continued for ≥2 weeks after knee arthroplasty and for 4 weeks after hip arthroplasty.

Rivaroxaban and apixaban were compared with enoxaparin for thromboprophylaxis in medically ill patients in the Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin (MAGELLAN) and Study of Apixaban for the Prevention of Thrombosis-Related Events in Patients With Acute Medical Illness (ADOPT) studies, respectively.[89,90] Neither study revealed a net benefit of extended thromboprophylaxis with a DOAC compared with a shorter course of enoxaparin, and the DOACs are not licensed for this indication. Using better risk stratification including an elevated plasma D-dimer level to identify the highest risk patients, betrixaban, another oral factor Xa inhibitor, is being compared with enoxaparin in the Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study (APEX) trial and rivaroxaban is being compared with placebo after hospital discharge in the A Study of Rivaroxaban (JNJ39039039) on the Venous Thromboembolic Risk in Posthospital Discharge Patients (MARINER) trial (Table 4).[91,92] These studies will determine the role of extended thromboprophylaxis with DOACs in the highest risk medically ill patients.

DOACs in Acute Coronary Syndrome

Patients remain at risk for major adverse cardiovascular events after ACS despite the routine use of dual-antiplatelet therapy with aspirin and an ADP receptor antagonist. Because ACS is triggered by thrombus formation at the site of a ruptured atherosclerotic plaque and there is evidence of increased thrombin generation for months after the index event,[93] the addition of an anticoagulant to antiplatelet therapy may further reduce the burden of recurrent major adverse cardiovascular events. Two DOACs, apixaban and rivaroxaban, were evaluated in placebo-controlled phase 3 randomized trials in stabilized ACS patients, most of whom were receiving dual-antiplatelet therapy. The Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (APPRAISE)-2 trial was stopped early because of an excess of major bleeding with apixaban (5 mg BID) compared with placebo (HR, 2.59; 95% CI, 1.50–4.46) and no evidence of a reduction in major adverse cardiovascular events (HR, 0.95; 95% CI, 0.80–1.11).[94] In contrast, in the Rivaroxaban in Patients With a Recent Acute Coronary Syndrome (ATLAS ACS)-2 Thrombolysis in Myocardial

Infarction (TIMI) 51 trial, rivaroxaban, at doses of 2.5 or 5 mg BID (doses lower than those used for stroke prevention in AF) reduced the rate of major adverse cardiovascular events (HR, 0.84; 95% CI, 0.74–0.96) and stent thrombosis (HR, 0.69; 95% CI, 0.51–0.93) compared with placebo in 15 526 stabilized ACS patients.[95] These benefits came at a cost of increased TIMI major bleeding (HR, 3.96; 95% CI, 2.46–6.38). With the lower 2.5 mg BID dose, rivaroxaban reduced cardiovascular mortality (HR, 0.66; 95% CI, 0.51–0.86) and all-cause mortality (HR, 0.68; 95% CI, 0.53–0.87) compared with placebo. Consequently, rivaroxaban 2.5 mg BID is licensed in Europe but not in North America for secondary prevention in stabilized ACS patients who presented with elevated cardiac biomarkers. Because rivaroxaban was not evaluated in combination with prasugrel or ticagrelor, it is only recommended in combination with clopidogrel.

Potential Mechanisms for the Factors That Differentiate DOACs From VKAs

The results from randomized clinical trials that compared the DOACs with VKAs in over 100 000 patients have identified ≥4 features that render the DOACs distinct from VKAs.[96] These include (1) the lower risk of intracranial hemorrhage, (2) the increased risk of gastrointestinal bleeding with the higher doses of all of the DOACs except apixaban, and (3) the potential for greater menstrual bleeding with rivaroxaban than with VKAs, and (4) the excess thromboembolic events with dabigatran in patients with mechanical heart valves. Each of these features is briefly discussed.

Intracranial Bleeding

The most feared complication of oral anticoagulant therapy is intracranial bleeding. The annual risk of intracranial bleeding with VKAs increases with age and can reach 1% in the elderly. Intracranial bleeding is associated with a 30-day mortality of 40% and those that survive may be left with sufficient disability to require long-term care.[97] Therefore, intracranial bleeding is the most devastating complication of anticoagulant therapy.

Compared with VKAs, the DOACs reduce the risk of intracranial hemorrhage by ≈50%.[11] This reduction reflects a decrease in both subdural and intracerebral bleeds. Furthermore, intracranial bleeds with the DOACs seem to be smaller in volume than those with VKAs, which likely explains why the case-fatality rate of intracranial bleeds with the DOACs is lower or similar to that with VKAs.[98,99]

Although the mechanistic explanation for the decreased risk of intracranial bleeding with the DOACs is uncertain, differences in the effect of DOACs and VKAs on thrombin generation may contribute. The brain is rich in tissue factor, and the cerebral blood vessels are surrounded by an envelope of tissue factor to ensure hemostasis.[100] Most of the thrombin generated in response to vascular injury is formed after fibrinogen is converted to fibrin. This late burst in thrombin generation is required to stabilize the fibrin network and endow it with its barrier properties. By lowering the levels of factor VII and the other vitamin K–dependent clotting proteins, VKAs not only delay thrombin generation but also markedly attenuate the postclotting thrombin burst. In contrast, although the DOACs also prolong the time to initiation of thrombin generation, they have only modest effects on the thrombin burst because their activity is limited to stoichiometric inhibition of factor Xa or thrombin.[101] With minimal effects on the thrombin burst, the DOACs may enable the generation of sufficient concentrations of thrombin to stabilize the fibrin network such that it prevents leakage of blood from the intravascular space. Additional work is needed to validate these concepts.

Gastrointestinal Bleeding

Bleeding with the DOACs seems to be organ bed specific.[96,100] Thus, the risk of intracranial bleeding with the DOACs is lower than that with warfarin, whereas the risk of gastrointestinal bleeding is higher at least with dabigatran at the 150 mg BID dose and with rivaroxaban and edoxaban at the 20 and 60 mg QD doses, respectively. Gastrointestinal bleeding with the DOACs seems to be dose related because the risk is similar to that with warfarin with the 110 mg BID dose of dabigatran and is significantly lower than that with warfarin with the 30-mg dose regimen of edoxaban. At the 5 mg BID dose of apixaban, the rate of gastrointestinal bleeding is similar to that with warfarin.

The explanation for the increase in gastrointestinal bleeding with the DOACs is uncertain. Unabsorbed drug is excreted in the feces and the presence of active anticoagulant in the gastrointestinal tract could trigger bleeding from ulcers, polyps, or other lesions.[12–15] Upper and lower gastrointestinal bleeding seem to occur with equal frequency with the DOACs, and an ongoing study (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease [COMPASS] study; Table 4) is evaluating the possibility that concomitant administration of a proton pump inhibitor may reduce the risk of bleeding from the upper gastrointestinal tract.[102] An analysis of the gastrointestinal bleeding with edoxaban suggests that even though the 60 mg QD dose was associated with more gastrointestinal bleeding than warfarin, the rates of life-threatening or fatal gastrointestinal bleeds were similar.[103] Therefore, fatal gastrointestinal bleeding with the DOACs is rare. Nonetheless, all patients who present with gastrointestinal bleeding with the DOACs should be evaluated for a potential source and this should be treated whenever possible so that anticoagulation therapy can be resumed.

Menstrual Bleeding

Rivaroxaban has been associated with increased uterine bleeding compared with warfarin.[104] It is unclear whether this problem occurs with the other DOACs.[105] Young women should be warned about this potential complication, and if it occurs, switching to the lower dose of the DOAC for the first few days of the menstrual cycle is usually sufficient for its control.

Thromboembolism and Mechanical Heart Valves

In the Phase II Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement trial, dabigatran was compared with warfarin in 2 groups of patients with mechanical heart valves; those with newly implanted valves and those with valves implanted >3 months before randomization.[106] Despite measurements of dabigatran levels and

dose-adjustment from 150 mg BID to a maximum of 300 mg BID to maintain trough drug levels >50 ng/mL, the study was stopped early because of an excess of thromboembolic events with dabigatran compared with warfarin (5% and 0%, respectively). These findings prompted black box warnings advising against the use of dabigatran and the other DOACs in patients with mechanical heart valves.

Although the explanation for the lack of efficacy of dabigatran in the RE-ALIGN study remains elusive, in vitro studies identify a potential mechanism.[107,108] Like catheters,[109] mechanical heart valves trigger clotting by activating factor XII, thereby inducing thrombin generation via the contact pathway. Because of multiple amplification steps, thrombin is generated in concentrations that overwhelm the local concentration of dabigatran, which inhibits thrombin in a 1:1 stoichiometric fashion. In contrast, by lowering the functional levels of the vitamin K–dependent clotting factors, warfarin attenuates thrombin generation regardless of the trigger. Supporting these assertions are the observations that warfarin attenuates thrombin generation induced by mechanical valves at INR values of ≥1.5, whereas dabigatran concentrations in excess of 260 ng/mL are required for equivalent suppression of thrombin generation.[107] These dabigatran concentrations are 5-fold higher than the targeted trough level of 50 ng/mL used in the RE-ALIGN study. It remains unknown whether by attenuating thrombin generation, rivaroxaban, apixaban, or edoxaban would be better than dabigatran for prevention of clotting on mechanical

Table 5. Safety and Efficacy Findings From Postmarketing Studies of Direct Oral Anticoagulants

Author/Study	Indication	Study Type	No. of Patients	Anticoagulants	Safety Outcome (Rates/y)	Efficacy Outcome (Rates/y)
Maura el al[111]	AF	Retrospective database	71 589	Rivaroxaban Dabigatran VKA	Major bleeding R 3.7% vs VKA 3.6% D 3.3% vs VKA 3.7%	Stroke+SEE R 1.4% vs VKA 1.5% D 2.0% vs VKA 1.8%
Camm et al[112]	AF	Prospective registry	6785	Rivaroxaban	Major bleeding 2.1%	Stroke+SEE 0.8%
Villines et al[113]	AF	Retrospective database	25 586	Dabigatran VKA	Major bleeding D 3.08% vs VKA 3.70%	Stroke D 0.92% vs VKA 1.32%
Seeger et al[114]	AF	Retrospective database	38 378	Dabigatran VKA	Major bleeding D 4.42% vs VKA 6.17%	Stroke D 0.77% vs VKA 1.07%
Lauffenburger et al[115]	AF	Retrospective database	64 935	Dabigatran VKA	Clinically important bleeding D 3.02% vs VKA 4.86%	Ischemic stroke D 3.02% vs VKA 4.8%
Graham et al[127]	AF	Retrospective database	134 414	Dabigatran VKA	Major bleeding D 4.27% vs VKA 4.39%	Ischemic stroke D 1.13% vs VKA 1.39%
Abraham et al[116]	AF and non-AF	Retrospective database	92 816	Dabigatran Rivaroxaban VKA	GI bleeding for AF D 2.29% vs VKA 2.87% R 2.84% vs VKA 3.06%	NR
Hernandez et al[117]	AF	Retrospective database	9404	Dabigatran VKA	Major bleeding D 9.0% vs VKA 5.9%	NR
Tamayo et al[118]	AF	Retrospective database	27 467	Rivaroxaban	Major bleeding 2.86%	NR
Beyer-Westendorf et al[119]	AF and VTE	Prospective registry	1776	Rivaroxaban	Major bleeding for AF cohort 3.1% Major bleeding for VTE cohort 4.1%	NR
Larsen et al[120]	AF	Retrospecive registry	11 315	Dabigatran VKA	Major bleeding D 2.1% to 3.7% VKA 2.6% to 3.7%	NR
Vaughan Sarrazin et al[121]	AF	Retrospective database	85 344	Dabigatran VKA	Any bleeding D 14.6% vs VKA 10.6%	NR
Turpie et al[122]	VTE prevention in major orthopedic surgery	Prospective registry	17 701	Rivaroxaban Standard of care	Major bleeding R 0.40% vs SOC 0.34%	Symptomatic VTE R 0.89% vs SOC 1.35%
Beyer-Westendorf et al[123,124]	VTE prevention in major orthopaedic surgery	Retrospective registry	5061	Rivaroxaban Fondaparinux LMWH	Major bleeding R 2.9% vs F 4.9% vs L 7.0%	Symptomatic VTE R 2.1% vs F 5.1% vs L 4.1%

AF indicates atrial fibrillation (nonvalvular); D, dabigatran; F, fondaparinux; R, rivaroxaban; LMWH, low molecular weight heparin; SEE, systemic embolic event; SOC, standard of care; VKA, vitamin K antagonist; and VTE, venous thromboembolism.

heart valves. Additional studies are needed to address this possibility.[110]

Effectiveness of DOACs in the Real World

Because randomized clinical trials have stringent inclusion and exclusion criteria, their results may be less applicable to patients in usual clinical practice. Postmarketing data from prospective observational studies, registries, insurance claim databases, and pharmacovigilance networks suggest that the effectiveness and safety of the DOACs in practice are consistent with the findings of the clinical trials (Table 5).[111–124] Additional studies are ongoing, but the results observed to date have encouraged the uptake of the DOACs for the licensed indications.[125]

Maximizing the Benefits of DOACs in Clinical Practice

To translate the favorable results of the randomized trials into benefits for patients, it is important that DOACs are optimally used. Barriers to optimal use include restricted access to the drugs because of reimbursement issues, unwillingness to prescribe them, and poor utilization resulting from error or omission in patient selection, choice of dose, prescription dispensation and follow-up, as well as poor persistence and adherence.[126] Access to DOACs is limited in some countries and patient groups because of high acquisition costs. Although VKAs are less expensive, DOACs are cost-effective because they eliminate the burden of routine coagulation monitoring and dose adjustment and they reduce the risk of serious bleeding. These benefits are making their way into practice, and there are data suggesting that the DOACs have overtaken VKAs in the United States, Canada, and Europe.[57,125]

Some healthcare providers were unwilling to prescribe DOACs because of unfamiliarity or concerns about bleeding in the absence of specific reversal agents. This barrier was lifted with the recent licensing of idarucizumab for reversal of dabigatran.[36] Andexanet alfa, the reversal agent for rivaroxaban, apixaban, and edoxaban, is now undergoing phase 3 evaluation and could be licensed later this year.[37] Even in the absence of reversal agents, however, it is important to point out the case fatality rate in patients with major bleeding is lower with the DOACs than with VKAs, and the DOACs are associated with significantly less intracranial bleeding.[11] Therefore, the lack of specific reversal agents for the oral factor Xa inhibitors is not a valid reason to restrict their use.

Dose selection is critical for achieving the maximum benefit of the DOACs. Depending on the agent, regulators have provided clinicians with dosing recommendations defined by patient characteristics including advanced age, reduced renal function, low body weight, and concomitant administration of potent P-glycoprotein inhibitors; factors associated with increased drug exposure and increased bleeding risk (Table 3). Despite clear dosing recommendations, however, observational data suggest that the lower doses of the DOACs are overprescribed, potentially compromising the efficacy of DOACs in clinical practice.[127] Education is needed to reverse this trend.

Although routine coagulation monitoring is unnecessary with the DOACs, patients still require follow-up to ensure adherence and to watch for declining renal function.[53,128] Although data suggest that persistence and adherence are higher with the DOACs than with VKAs,[129,130] regular follow-up provides an opportunity for ongoing education, periodic evaluation of the bleeding risk, and review of concomitant medications.

New Opportunities for the DOACs

With successful approval and the use in the aforementioned indications, the DOACs are undergoing evaluation in numerous other indications including coronary or peripheral artery disease, embolic stroke of unknown source, postcoronary stenting in patients with AF, heart failure, cancer-associated VTE, and extended prophylaxis in the medically ill (Table 4).

Future Directions

The DOACs represent a major advance in oral anticoagulation. Nonetheless, gaps persist. For example, more information is needed about the efficacy and safety of the DOACs in patients with impaired renal function (creatinine clearance between 15 and 30 mL/min) because such patients were excluded from the clinical trials. In addition, the optimal dosing of DOACs in patients with morbid obesity and in pediatric patients remains uncertain.

The DOACs have not succeeded in all indications. Thus, dabigatran was less effective than warfarin for stroke prevention in patients with mechanical heart valves, and it is unknown whether oral factor Xa inhibitors will fare any better for this indication.[106] Medical devices, such as heart valves, trigger clotting by activating factor XII and may locally generate factor Xa and thrombin in concentrations that exceed those of the DOACs.[107,108] Ongoing research is investigating the use of inhibitors of factor XII or XI to address this unmet need.[131]

Conclusions

The DOACs are at least as effective, safer, and more convenient than VKAs and are revolutionizing our approach to prevention and treatment of thromboembolism. Postmarketing studies suggest that although the favorable results of clinical trials can readily be translated into practice, there remains a need for selection of the appropriate patient, drug and dose, and careful follow-up. Leveraging on their favorable results in AF and in VTE prevention and treatment and building on the mechanistic insights gained from these trials, DOACs are now being evaluated for multiple new indications. Therefore, the use of the DOACs is likely to continue to increase.

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