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STATE-OF-THE-ART REVIEW

Direct Oral Anticoagulants

New Drugs and New Concepts

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) describe the mechanism of action, pharmacokinetics and pharmacodynamics of direct oral anticoagulants; 2) compare the efficacy and bleeding risks between the different direct oral anticoagulants and with warfarin; and 3) identify the best direct oral anticoagulant to use in situations such as renal or hepatic impairment.

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Direct Oral Anticoagulants

New Drugs and New Concepts

ABSTRACT

Direct oral anticoagulants (DOACs) are approved for multiple thromboembolic disorders and provide advantages over existing agents. As with all anticoagulants, management protocols for the eventuality of bleeding are important. Randomized phase III studies generally show that DOACs have a similar risk of clinically relevant bleeding compared with standard anticoagulants, with reductions in major bleeding in some cases. This may be particularly important in patients with atrial fibrillation, for whom the rate of intracranial hemorrhage was approximately halved with DOACs compared with warfarin. Conversely, the risk of gastrointestinal bleeding may be increased. Specific patient characteristics, such as renal impairment, comedications, and particular aspects of each drug, including the proportion eliminated by the kidneys, must be taken into account when assessing the risk of bleeding. Although routine coagulation monitoring of DOACs is not required, it may be useful under some circumstances. Of the traditional clotting assays, a sensitive and calibrated prothrombin time may be useful for detecting the presence or absence of clinically relevant factor Xa inhibitor concentrations (rivaroxaban or apixaban), but specific anti–factor Xa assays can measure drug levels quantitatively. For dabigatran, the results of an activated partial thromboplastin time test may exclude a clinically relevant pharmacodynamic effect, but a calibrated dilute thrombin time assay can be used for quantification of drug levels. In the event of mild or moderate bleeding, normal hemostatic support measures are recommended. For life-threatening bleeding, use of nonspecific prohemostatic agents may be considered, although clinical evidence is scarce. Specific antidotes are in development. (J Am Coll Cardiol Intv 2014;7:1333–51) © 2014 by the American College of Cardiology Foundation.

Several direct oral anticoagulants (DOACs), namely, apixaban (1,2), rivaroxaban (3,4), and dabigatran etexilate (5,6), are currently licensed in Europe and the United States for various thromboembolic indications. A fourth DOAC, edoxaban, has also demonstrated efficacy and safety in venous thromboembolism (VTE) treatment and stroke prevention in patients with atrial fibrillation (AF) (7,8), but is not licensed in Europe or the United States.

The DOACs have a rapid onset (~2 to 4 h) and offset (~24 h) of action with normal renal function (9,10). They provide alternatives to low molecular weight heparin (LMWH) in a peri-operative setting for VTE prophylaxis and therapy and to vitamin K antagonists (VKAs) for longer term therapy. Because the DOACs have predictable pharmacokinetic/pharmacodynamic effects, routine coagulation monitoring for titration and maintenance is not required (11). However, if patients experience bleeding or need procedural interventions, laboratory monitoring can be performed. Although there are currently no specific reversal agents available to manage life-threatening bleeding with DOACs, most anticoagulants are not acutely reversible, except for unfractionated heparin with protamine (12). VKAs are acutely reversible with 4-component prothrombin complex concentrates (PCCs), including 1 recently approved in the United States (prothrombin complex concentrate), but there is no specific reversal agent for LMWHs, which may accumulate in patients with renal dysfunction (13). For all anticoagulants, management protocols for potential bleeding should be established. Clinical studies with the DOACs for current indications have provided extensive safety data. This review summarizes current and evolving data for the DOACs and management strategies for bleeding, when it occurs.

THERAPEUTIC AND BLEEDING PROFILES OF DOACS IN CLINICAL STUDIES

APIXABAN. Apixaban, a direct factor Xa inhibitor, is widely approved for thromboprophylaxis in elective hip or knee replacement surgery (1,14) and for stroke prevention in patients with nonvalvular AF (**Table 1**) (1,2).

For VTE prophylaxis, apixaban, initiated 12 to 24 h postoperatively, was compared with enoxaparin for preventing VTE in elective hip/knee replacement surgery (ADVANCE studies) (15–17). In ADVANCE-1 (Apixaban Dosed Orally Versus Anti-coagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism), apixaban did not demonstrate noninferiority for efficacy compared with enoxaparin 30 mg twice daily (bid) when given after knee replacement surgery (15). However, apixaban was superior to enoxaparin 40 mg once daily (qd) in

ADVANCE-2 when given after knee replacement surgery (16), and in ADVANCE-3 (Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism-3) after hip replacement surgery (17). Major bleeding and clinically relevant bleeding occurred at a similar rate between the treatment groups in these studies (**Table 2**) (15–17). Apixaban has been compared with LMWH plus warfarin in a randomized phase III study for treating acute VTE (AMPLIFY [Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy]) (**Table 3**) (18). Overall, there was a significantly lower incidence of major and nonmajor clinically relevant bleeding with apixaban (4.3% vs. 9.7%; $p < 0.001$) (18). A 12-month extension study (AMPLIFY-EXT [Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment]) compared apixaban 2.5 mg or 5 mg bid with placebo for the secondary prevention of recurrent VTE in patients who had already received 6 to 12 months of anticoagulation treatment (19). There was a similar incidence of major bleeding with both doses (**Table 4**). Rates of clinically relevant bleeding were numerically higher with active treatment (3.2% and 4.3% vs. 2.7%, respectively; p values nonsignificant for all comparisons), but rates of all-cause mortality were lower (0.8% and 0.5% vs. 1.7%, respectively) (19).

Long-term apixaban 5 mg bid was compared with acetylsalicylic acid (ASA) and warfarin in 2 separate trials for the prevention of stroke and systemic embolism in patients with nonvalvular AF (AVERROES [Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment] and ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation], respectively) (20,21). Apixaban was superior to warfarin in terms of major and nonmajor clinically relevant bleeding ($p < 0.001$) and all-cause mortality ($p = 0.047$) (**Table 5**). Rates of major gastrointestinal bleeding were similar with apixaban and both comparators, and there was significantly less intracranial bleeding with apixaban compared with warfarin (0.3%/year vs. 0.8%/year; $p < 0.001$) (20,21).

Apixaban in combination with standard antiplatelet therapy was compared with antiplatelet therapy alone in patients with recent acute coronary syndrome (ACS) (APPRAISE-2 [Apixaban for Prevention of Acute Ischemic Events-2]) (22). However, the risk of bleeding outweighed the clinical benefit of anticoagulation in these patients, and the trial was stopped early.

RIVAROXABAN. Rivaroxaban is a direct factor Xa inhibitor and is licensed in the European Union and North America for: 1) the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE); 2) the prevention of recurrent DVT and PE in adults; 3) thromboprophylaxis in adults undergoing elective hip or knee replacement surgery; and 4) the prevention of stroke and systemic embolism in adults with nonvalvular AF (3,4). In the European Union, rivaroxaban has been approved (at a dose of 2.5 mg bid), in combination with ASA alone or ASA plus clopidogrel or ticlopidine to prevent atherothrombotic events in patients with ACS and elevated cardiac biomarkers (**Table 1**) (3).

The phase III RECORD (REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) program evaluated the use of rivaroxaban for VTE prophylaxis in patients undergoing elective total hip or knee replacement surgery and consisted of 4 trials of rivaroxaban 10 mg qd (started 6 to 8 h after surgery) compared with 2 standard subcutaneous enoxaparin regimens (30 mg bid initiated after surgery and 40 mg qd initiated before surgery) (23–26). Rivaroxaban was superior to enoxaparin 30 mg bid and 40 mg qd for VTE prevention, with a similar incidence of major bleeding (**Table 2**) (23–28). However, bleeding at the surgical site was not classified as major bleeding but was included as part of a composite of major and nonmajor clinically relevant bleeding. In a pooled analysis of the 4 trials, major and nonmajor clinically relevant bleeding occurred more frequently with rivaroxaban than with enoxaparin over the total treatment duration (3.2% vs. 2.6%; $p = 0.04$) but not during the 12 ± 2 days of active treatment (2.9% vs. 2.5%; $p = 0.19$) (29).

Three phase III randomized studies of rivaroxaban in the VTE treatment setting were conducted (30,31). In the EINSTEIN DVT and EINSTEIN PE trials, rivaroxaban was noninferior to standard enoxaparin/VKA treatment in patients who had acute DVT (without PE) (30) and PE (with or without DVT) (31), respectively. In the EINSTEIN EXT, extended rivaroxaban treatment was superior to placebo for the prevention of recurrent VTE in patients already successfully treated for an initial VTE and for whom the benefit-risk balance of continuing or stopping treatment was unclear (30). In the EINSTEIN DVT and EINSTEIN EXT, there was no significant difference in major bleeding between rivaroxaban and the comparator

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AF = atrial fibrillation
ASA = acetylsalicylic acid
bid = twice daily
CrCl = creatinine clearance
CYP = cytochrome P450
DOAC = direct oral anticoagulant
DVT = deep venous thrombosis
ICH = intracranial hemorrhage
INR = international normalized ratio
LMWH = low molecular weight heparin
PCC = prothrombin complex concentrate
PE = pulmonary embolism
P-gp = P-glycoprotein
PT = prothrombin time
qd = once daily
VKA = vitamin K antagonist
VTE = venous thromboembolism

TABLE 1 Summary of Pharmacokinetic and Pharmacodynamic Characteristics of Direct Oral Anticoagulants (1-6,45)

Anticoagulant	Target	Approved Indications*	Onset of Action (t_{max}, h)	$t_{1/2}$, h	Offset of Action, h	Method of Excretion	Food Effect	Drug Interactions	Dose Adjustments
Apixaban	Factor Xa	VTE prevention in patients undergoing elective hip or knee replacement surgery (2.5 mg bid)* Prevention of stroke/systemic embolism in patients with nonvalvular AF (5 mg bid)	3-4	~12	24-48	Hepatobiliary: 73% Active renal secretion: 27%	None	Avoid strong CYP3A4 and P-gp inhibitors† Caution with strong CYP3A4 inducers	Stroke prevention: 2.5 mg bid in patients with at least 2 of the following: age ≥80 yrs, weight ≤60 kg, serum creatinine ≥1.5 mg/dl or ≥133 μmol/l,* or receiving strong CYP3A4 and P-gp inhibitors‡ In patients already taking 2.5-mg bid dose, avoid strong CYP3A4 and P-gp inhibitors‡
Rivaroxaban	Factor Xa	VTE prevention in patients undergoing elective hip or knee replacement surgery (10 mg qd) Prevention of stroke/systemic embolism in patients with nonvalvular AF (20 mg qd) Treatment of DVT/PE and prevention of recurrent VTE (15 mg bid for 21 days, then 20 mg qd) Prevention of atherothrombotic events in adult patients with elevated cardiac biomarkers after an acute coronary syndrome (2.5 mg bid combined with standard antiplatelet therapy)†	2-4	5-13	24-48	Hepatobiliary: 66% Active renal secretion: 33% Renal elimination of inactive metabolites: 33%	Take 15- and 20-mg doses with food	Avoid strong CYP3A4 and P-gp inhibitors Caution with strong CYP3A4 inducers	Stroke prevention: 15 mg qd in patients with CrCl 15-49 ml/min
Edoxaban	Factor Xa	None currently	1-3	9-11	No data	Hepatobiliary: 50% Active renal secretion: 50%	Not expected to be clinically relevant	No current recommendation	Reduced doses tested in clinical studies for patients with CrCl 30-50 ml/min or body weight ≤60 kg or receiving concomitant strong P-gp inhibitors
Dabigatran	Thrombin	VTE prevention in patients undergoing elective hip or knee replacement surgery (220 mg qd)† Prevention of stroke/systemic embolism in patients with nonvalvular AF (150 mg bid)	0.5-2	12-17	24-96	Hepatobiliary: 20% Active renal secretion: 80%	Taking with food delays t_{max} by ~2 h	Avoid strong P-gp inhibitors or inducers	VTE prevention: 150 mg qd in patients with CrCl 30-50 ml/min or for reasons of age ≥75 years or the risk of drug interactions Stroke prevention: 110 mg† bid/ 75 mg‡ bid for reasons of age ≥80 years or the risk of drug interactions

*Europe and North America. †Europe only. ‡United States only.

AF = atrial fibrillation; bid = twice daily; CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; DVT = deep venous thrombosis; PE = pulmonary embolism; P-gp = P-glycoprotein; qd = once daily; $t_{1/2}$ = half-life; t_{max} = time to maximal concentration; VTE = venous thromboembolism.

TABLE 2 Efficacy and Bleeding Outcomes in Phase III Clinical Studies of Direct Oral Anticoagulants for the Prevention of Venous Thromboembolism after Total Hip and Knee Replacement Surgery

Study Name (Ref. #)	Design	Patients (Number Randomized)	Study Arms	Treatment Duration	Primary Efficacy Outcome	Primary Bleeding Outcome	Other Bleeding Outcomes
ADVANCE-1 (15)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Undergoing elective total knee replacement (N = 3,195)	Apixaban oral 2.5 mg bid or enoxaparin sc 30 mg bid	10–14 days	VTE plus all-cause death: 9.0% vs. 8.8% (p = 0.06 for noninferiority)	Major bleeding: 0.7% vs. 1.4% (p = 0.053)	Major and nonmajor clinically relevant bleeding: 2.9% vs. 4.3% (p = 0.03)
ADVANCE-2 (16)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Undergoing elective total knee replacement (N = 3,057)	Apixaban oral 2.5 mg bid or enoxaparin sc 40 mg qd	10–14 days	VTE plus all-cause death: 15.1% vs. 24.4% (p < 0.0001)	Major bleeding: 0.6% vs. 0.9% (p = 0.3014)	Major and nonmajor clinically relevant bleeding: 3.5% vs. 4.8% (p = 0.0881)
ADVANCE-3 (17)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Undergoing elective total hip replacement (N = 5,407)	Apixaban oral 2.5 mg bid or enoxaparin sc 40 mg qd	32–38 days	VTE plus all-cause death: 1.4% vs. 3.9% (p < 0.001)	Major bleeding: 0.8% vs. 0.7% (p = 0.54)	Major and nonmajor clinically relevant bleeding: 4.8% vs. 5.0% (p = 0.72)
RECORD1 (23)	Multicenter, randomized, double-blind, double-dummy, active-control, superiority	Age ≥18 yrs undergoing elective total hip replacement (N = 4,541)	Rivaroxaban oral 10 mg qd or enoxaparin sc 40 mg qd	5 weeks	VTE plus all-cause death: 1.1% vs. 3.7% (p < 0.001)	Major bleeding: 0.3% vs. 0.1% (p = 0.18)	Major and nonmajor clinically relevant bleeding: 3.2% vs. 2.5% (p = NS)
RECORD2 (24)	Multicenter, randomized, double-blind, double-dummy, active-control, superiority	Age ≥18 yrs undergoing elective total hip replacement (N = 2,509)	Rivaroxaban oral 10 mg qd or enoxaparin sc 40 mg qd	31–39 days (rivaroxaban) or 10–14 days (enoxaparin)	VTE plus all-cause death: 2.0% vs. 9.3% (p < 0.0001)	Major bleeding: <0.1% vs. <0.1%	Any on-treatment bleeding: 6.6% vs. 5.5% (p = 0.25)
RECORD3 (25)	Multicenter, randomized, double-blind, double-dummy, active-control, superiority	Age ≥18 yrs undergoing elective total knee replacement (N = 2,531)	Rivaroxaban oral 10 mg qd or enoxaparin sc 40 mg qd	10–14 days	VTE plus all-cause death: 9.6% vs. 18.9% (p < 0.001)	Major bleeding: 0.6% vs. 0.5% (p = 0.77)	Any on-treatment bleeding: 4.9% vs. 4.8% (p = 0.93)
RECORD4 (26)	Multicenter, randomized, double-blind, double-dummy, active-control, superiority	Age ≥18 yrs undergoing elective total knee replacement (N = 3,148)	Rivaroxaban oral 10 mg qd or enoxaparin sc 30 mg bid	10–14 days	VTE plus all-cause death: 6.9% vs. 10.1% (p = 0.0118)	Major bleeding: 0.7% vs. 0.3% (p = 0.1096)	Major and nonmajor clinically relevant bleeding: 3.0% vs. 2.3% (p = 0.1790)
RE-NOVATE (34)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs undergoing elective total hip replacement (N = 3,494)	Dabigatran etexilate oral 150 or 220 mg qd (half-quantity first dose) or enoxaparin sc 40 mg qd	28–35 days	VTE plus all-cause death: 8.6% and 6.0% vs. 6.7% (p < 0.0001 for noninferiority)	Major bleeding: 1.3% and 2.0% vs. 1.6% (p = 0.60 and p = 0.44 vs. enoxaparin)	Nonmajor clinically relevant bleeding: 4.7% and 4.2% vs. 3.5%
RE-NOVATE II (35)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs undergoing elective total hip replacement (N = 2,055)	Dabigatran etexilate oral 220 mg qd (half-quantity first dose) or enoxaparin sc 40 mg qd	28–35 days	VTE plus all-cause death: 7.7% vs. 8.8% (p < 0.0001 for noninferiority)	Major bleeding: 1.4% vs. 0.9% (p = 0.40)	Major or nonmajor clinically relevant bleeding: 3.7% vs. 2.9% (p = 0.33)
RE-MODEL (36)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs undergoing elective total knee replacement (N = 2,101)	Dabigatran etexilate oral 150 or 220 mg qd (half-quantity first dose) or enoxaparin sc 40 mg qd	6–10 days	VTE plus all-cause death: 40.5% and 36.4% vs. 37.7% (p = 0.017 and p = 0.0003 for noninferiority)	Major bleeding: 1.3% and 1.5% vs. 1.3% (p = 1.0 and p = 0.82 vs. enoxaparin)	Nonmajor clinically relevant bleeding: 6.8% and 5.9% vs. 5.3%
RE-MOBILIZE (37)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs undergoing elective total knee replacement (N = 2,615)	Dabigatran etexilate oral 150 or 220 mg qd (half-quantity first dose) or enoxaparin sc 30 mg bid	12–15 days	VTE plus all-cause death: 33.7% and 31.1% vs. 25.3% (p < 0.001 and p = 0.02 in favor of enoxaparin)	Major bleeding: 0.6% and 0.6% vs. 1.4%	Nonmajor clinically relevant bleeding: 2.5% and 2.7% vs. 2.4%

ADVANCE-1 = Apixaban Dosed Orally Versus Anti-coagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism-1; ADVANCE-3 = Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism-3; NS = nonsignificant; RECORD = REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism; RE-MODEL = Dabigatran Etexilate 150 mg or 220 mg Once Daily (o.d.) Versus (v.s.) Enoxaparin 40 mg o.d. for Prevention of Thrombosis After Knee Surgery; RE-NOVATE = Dabigatran Etexilate in Extended Venous Thromboembolism (VTE) Prevention After Hip Replacement Surgery; RE-NOVATE II = Dabigatran Etexilate Compared With Enoxaparin in Prevention of Venous Thromboembolism (VTE) Following Total Hip Arthroplasty; sc = subcutaneous; other abbreviations as in Table 1.

TABLE 3 Bleeding Outcomes in Phase III Clinical Studies of Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism

Study Name (Ref. #)	Design	Patients (Number Randomized)	Study Arms	Treatment Duration	Primary Efficacy Outcome	Primary Bleeding Outcome	Other Bleeding Outcomes
AMPLIFY (18)	Multicenter, randomized, double-blind, noninferiority	Age ≥18 yrs with confirmed proximal DVT or symptomatic PE with or without DVT (N = 5,400)	Apixaban oral 10 mg bid for 7 days followed by 5 mg bid or enoxaparin sc 1.0 mg/kg bid for ≥5 days plus VKA started ≤48 h after randomization	6 months	Recurrent, symptomatic VTE or VTE-related death: 2.3% vs. 2.7% ($p < 0.001$ for noninferiority)	Major bleeding: 0.6% vs. 1.8% ($p < 0.001$)	Major and nonmajor clinically relevant bleeding: 4.3% vs. 9.7% ($p < 0.001$)
EINSTEIN DVT (30)	Multicenter, randomized, open-label, event-driven, active control, noninferiority	Age ≥18 yrs with confirmed proximal DVT without symptomatic PE (N = 3,449)	Rivaroxaban oral 15 mg bid for 3 weeks followed by 20 mg qd or enoxaparin sc 1.0 mg/kg bid for ≥5 days plus VKA started ≤48 h after randomization	3, 6, or 12 months	Recurrent VTE: 2.1% vs. 3.0% ($p < 0.001$ for noninferiority)	Major and nonmajor clinically relevant bleeding: 8.1% vs. 8.1% ($p = 0.77$)	Major bleeding: 0.8% vs. 1.2% ($p = 0.21$)
EINSTEIN PE (31)	Multicenter, randomized, open-label, event-driven, active control, noninferiority	Age ≥18 yrs with confirmed acute symptomatic PE with or without DVT (N = 4,832)	Rivaroxaban oral 15 mg bid for 3 weeks followed by 20 mg qd or enoxaparin sc 1.0 mg/kg bid for ≥5 days plus VKA started ≤48 h after randomization	3, 6, or 12 months	Recurrent, symptomatic VTE: 2.1% vs. 1.8% ($p = 0.003$ for noninferiority)	Major or nonmajor clinically relevant bleeding: 10.3% vs. 11.4% ($p = 0.23$)	Major bleeding: 1.1% vs. 2.2% ($p = 0.003$)
RE-COVER (38)	Multicenter, randomized, double-blind, double-dummy, active control, noninferiority	Age ≥18 yrs with acute, symptomatic VTE and eligible for 6 months of anticoagulant therapy (N = 2,564)	Induction with a parenteral anticoagulant followed by dabigatran etexilate oral 150 mg bid vs. warfarin oral (INR, 2.0-3.0) qd	6 months	Recurrent, symptomatic VTE or VTE-related death: 2.4% vs. 2.1% ($p < 0.001$ for noninferiority)	Major bleeding: 1.6% vs. 1.9% (HR: 0.82; 95% CI: 0.45–1.48)	Major or nonmajor clinically relevant bleeding: 5.6% vs. 8.8% (HR: 0.63; 95% CI: 0.47–0.84)
RE-COVER II (39)	Multicenter, randomized, double-blind, double-dummy, active control, noninferiority	Age ≥18 yrs with acute, symptomatic VTE (N = 2,568)	Induction with a parenteral anticoagulant followed by dabigatran etexilate oral 150 mg bid vs. warfarin oral (INR, 2.0-3.0) qd	6 months	Recurrent, symptomatic VTE or VTE-related death: 2.3% vs. 2.2% ($p < 0.001$ for noninferiority)	Major bleeding: 1.2% vs. 1.7% (HR: 0.69; 95% CI: 0.36–1.32)	Any bleeding: 15.6% vs. 22.1% (HR: 0.67; 95% CI: 0.56–0.81)
Hokusai-VTE (8)	Multicenter, randomized, double-blind, active control, non-inferiority	Age ≥18 yrs with acute, symptomatic VTE (N = 8,240)	Induction with sc heparin followed by edoxaban oral 60 mg qd* vs. warfarin qd (INR, 2.0-3.0)	3-12 months	Recurrent, symptomatic VTE: 3.2% vs. 3.5% ($p < 0.001$ for noninferiority)	Major or nonmajor clinically relevant bleeding: 8.5% vs. 10.3% ($p = 0.004$)	Major bleeding: 1.4% vs. 1.6% ($p = 0.35$)

*30 mg qd in patients with creatinine clearance 30 to 50 ml/min, body weight ≤60 kg, or receiving concomitant treatment with a potent P-glycoprotein inhibitor.

AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II = Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp Venous Thromboembolism (VTE); VKA = vitamin K antagonist; other abbreviations as in Tables 1 and 2.

regimen (**Tables 3 and 4**); however, in the EINSTEIN PE, rivaroxaban treatment led to a significant 51% relative risk reduction in major bleeding compared with enoxaparin/VKA (**Table 3**) (31). In both acute treatment studies, major bleeding in a critical site, associated with a decrease in hemoglobin of ≥2 g/dl and/or transfusion of ≥2 units of blood, or leading to death, occurred with an incidence of <1% in the rivaroxaban arms (30,31). In the EINSTEIN PE, there were fewer cases of major bleeding at a critical site, especially intracranial and retroperitoneal bleeding, with rivaroxaban than with enoxaparin/VKA (31).

Further data on the long-term use of rivaroxaban 20 mg qd were provided by the 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) study, in which rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF, and rivaroxaban did not increase the rate of clinically relevant bleeding (14.9%/year vs. 14.5%/year; p = 0.44) (**Table 5**) (32). Rivaroxaban was associated with significant reductions in the annual rates of intracranial hemorrhage (ICH) (0.5% vs. 0.7%; p = 0.02), critical site bleeding (0.8% vs. 1.2%; p = 0.007), and fatal bleeding (0.2% vs. 0.5%; p = 0.003) compared with warfarin, set against an increase in gastrointestinal bleeding (3.2% vs. 2.2%; p < 0.001), major bleeding associated with a ≥2 g/dl decrease in hemoglobin (2.8% vs. 2.3%; p = 0.02), and major bleeding requiring blood transfusion (1.6% vs. 1.3%; p = 0.04) (**Table 5**) (32).

In the ATLAS ACS-2 TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis In Myocardial Infarction 51) study, rivaroxaban 2.5 mg or 5 mg bid in combination with standard antiplatelet therapy (ASA with or without a thienopyridine) was compared with antiplatelet therapy alone in patients with recent ACS (33). Rivaroxaban significantly reduced the incidence of death of cardiovascular causes, myocardial infarction, or stroke (p = 0.008 across both doses compared with antiplatelet therapy alone), but also led to a significant increase in major bleeding not related to coronary artery bypass grafting (2.1% vs. 0.6%, respectively; p < 0.001) and in ICH (0.6% vs. 0.2%, respectively; p = 0.009). However, fatal bleeding was not significantly increased (0.3% vs. 0.2%, respectively; p = 0.66). Overall, the 2.5-mg

TABLE 4 Bleeding Outcomes in Phase III Clinical Studies of Long-Term Treatment With Direct Oral Anticoagulants for the Prevention of Recurrent Venous Thromboembolism

Study Name (Ref. #)	Design	Patients (Number Randomized)	Study Arms	Treatment Duration	Primary Efficacy Outcome	Primary Bleeding Outcome	Other Bleeding Outcomes
AMPLIFY-EXT (19)	Multicenter, randomized, double-blind, placebo-controlled, superiority	Age ≥18 yrs who had completed 6–12 months of treatment for previous VTE (N = 2,486)	Apixaban oral 2.5 or 5 mg bid vs. placebo	12 months	Recurrent, symptomatic VTE or all-cause death: 3.8% and 4.2% vs. 11.6% (p < 0.001)	Major bleeding: 0.2% and 0.1% vs. 0.5% (p = NS for both comparisons)	Major or nonmajor clinically relevant bleeding: 3.2% and 4.3% vs. 2.7% (p = NS for both comparisons)
EINSTEIN EXT (30)	Multicenter, randomized, double-blind, event-driven, placebo-controlled, superiority	Age ≥18 yrs who had received 6–12 months of anticoagulant therapy for VTE (N = 1,197)	Rivaroxaban oral 20 mg qd or placebo	6 or 12 months	Recurrent VTE: 1.3% vs. 7.1% (p < 0.001)	Major bleeding: 0.7% vs. 0.0% (p = 0.11)	Major or nonmajor clinically relevant bleeding: 6.0% vs. 1.2% (p < 0.001)
RE-MEDY (40)	Multicenter, randomized, double-blind, double-dummy, active control, non-inferiority	Patients who had completed 3–12 months of anticoagulant therapy for VTE (N = 2,866)	Dabigatran etexilate oral 150 mg bid vs. warfarin oral (INR, 2.0–3.0) qd	6–36 months	Recurrent VTE or VTE-related death: 1.8% vs. 1.3% (p = 0.01 for noninferiority)	Major bleeding: 0.9% vs. 1.8% (HR: 0.52; 95% CI: 0.27–1.02)	Major or clinically relevant bleeding: 5.6% vs. 10.2% (p < 0.001)
RE-SONATE (40)	Multicenter, randomized, double-blind, double-dummy, placebo-controlled, superiority	Patients who had completed 6–18 months of anticoagulant therapy for VTE (N = 1,353)	Dabigatran etexilate oral 150 mg bid or placebo	6 months	Recurrent VTE or VTE-related/unexplained death: 0.4% vs. 5.6% (p < 0.001)	Major bleeding: 0.3% vs. 0.0% (p = NS)	Major or clinically relevant bleeding: 5.3% vs. 1.8% (p = 0.001)

AMPLIFY-EXT = Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment; RE-MEDY = Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE = Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; other abbreviations as in **Tables 1 to 3**.

TABLE 5 Bleeding Outcomes in Phase III Clinical Studies of Long-Term Therapy With Direct Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Study Name (Ref. #)	Design	Patients (Number Randomized)	Study Arms	Treatment Duration	Primary Efficacy Outcome	Primary Bleeding Outcome	Other Bleeding Outcomes
AVERROES (20)	Multicenter, randomized, double-blind, active-controlled, superiority	Age ≥50 yrs with AF and ≥1 risk factors for stroke who met the criteria for, but were not suitable for, warfarin (N = 5,599)	Apixaban oral 2.5 or 5 mg bid vs. ASA oral 81–324 mg qd	Median 1.1 yrs	Stroke or systemic embolism: 1.6% vs. 3.7%/yr ($p < 0.001$)	Major bleeding: 1.4% vs. 1.2%/yr ($p = 0.57$)	ICH: 0.4% vs. 0.4%/yr ($p = 0.69$) GI bleeding: 0.4% vs. 0.4%/yr ($p = 0.71$)
ARISTOTLE (21)	Multicenter, randomized, double-blind, active-controlled, noninferiority/ superiority	Patients with AF with ≥1 risk factors for stroke (N = 18,201)	Apixaban oral 2.5 or 5 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 1.8 yrs	Stroke or systemic embolism: 1.3% vs. 1.6%/yr ($p = 0.01$ for superiority)	Major bleeding: 2.1% vs. 3.1%/yr ($p < 0.001$)	Major or nonmajor clinically relevant bleeding: 4.1% vs. 6.0%/yr ($p < 0.001$) Major intracranial bleeding: 0.3% vs. 0.8%/yr ($p < 0.001$) Major GI bleeding: 0.8% vs. 0.9%/yr ($p = 0.37$)
ROCKET AF (32)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs with AF at moderate to high risk of stroke (N = 14,264)	Rivaroxaban oral 20 mg qd (15 mg qd in patients with CrCl 30–49 ml/min) or warfarin adjusted to maintain an INR of 2.0–3.0	Median 590 days	Stroke or systemic embolism: 1.7% vs. 2.2% ($p < 0.001$ for noninferiority)	Major and nonmajor clinically relevant bleeding: 14.9% vs. 14.5%/yr ($p = 0.44$)	Major bleeding: 3.6% vs. 3.4%/yr ($p = 0.58$) ICH: 0.5% vs. 0.7%/yr ($p = 0.02$) Fatal bleeding: 0.2% vs. 0.5%/yr ($p = 0.003$) GI bleeding: 3.2% vs. 2.2% ($p < 0.001$)
RE-LY (41)	Multicenter, randomized, single-blind, active control, noninferiority	Age ≥18 yrs with AF and ≥1 risk factors for stroke (N = 18,113)	Dabigatran etexilate oral 110 or 150 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 2 yrs	Stroke or systemic embolism: 1.5% and 1.1%/yr vs. 1.7%/yr ($p < 0.001$ for noninferiority and superiority, respectively)	Major bleeding: 2.7% and 3.1% vs. 3.4%/yr ($p = 0.003$ and $p = 0.31$ vs. warfarin)	Any bleeding: 14.6% and 16.4% vs. 18.2%/yr ($p < 0.001$ and $p = 0.002$ vs. warfarin) ICH: 0.23% and 0.30% vs. 0.74%/yr ($p < 0.001$ vs. warfarin) GI bleeding: 1.1% and 1.5% vs. 1.0%/year ($p = 0.43$ and $p < 0.001$ vs. warfarin) Life-threatening bleeding: 1.2% and 1.5% vs. 1.8% ($p < 0.001$ and $p = 0.04$ vs. warfarin)
RELY-ABLE (42)	Multicenter, double-blind, extension, descriptive	Patients who completed RE-LY without drug discontinuation (N = 5,851*)	Dabigatran etexilate oral 150 or 110 mg bid	Median 28 months	Stroke or systemic embolism: 1.5% vs. 1.6% (HR: 0.91; 95% CI: 0.69–1.20)	Major bleeding: 3.7% vs. 3.0%/year (HR: 1.26; 95% CI: 1.04–1.53)	Life-threatening bleeding: 1.8% vs. 1.6%/year (HR: 1.14; 95% CI: 0.87–1.49) Fatal bleeding: 0.2% vs. 0.3%/yr (HR: 0.94; 95% CI: 0.46–1.89) ICH: 0.3% vs. 0.3%/yr (HR: 1.31; 95% CI: 0.68–2.51) GI bleeding: 1.5% vs. 1.6%/yr (HR: 0.99; 95% CI: 0.75–1.31)

Continued on the next page

TABLE 5 Continued

Study Name (Ref. #)	Design	Patients (Number Randomized)	Study Arms	Treatment Duration	Primary Efficacy Outcome	Primary Bleeding Outcome	Other Bleeding Outcomes
Engage AF-TIMI 48 (7)	Multicenter, randomized, double-blind, active control, noninferiority	Age ≥21 yrs with AF confirmed for 12 months and $CHADS_2$ ≥2 (N = 21,105)	Edoxaban oral 30 mg or 60 mg qd† vs. oral warfarin qd (INR 2.0–3.0)	Median 2.8 yrs	Stroke or systemic embolism: 1.6% and 1.2%/yr vs. 1.5%/yr ($p = 0.005$ and $p < 0.001$ for noninferiority, respectively)	Major bleeding: 1.6% and 2.8%/yr vs. 3.4%/yr ($p < 0.001$ for both doses)	Death or ICH: 4.0% and 4.3%/yr vs. 4.9%/yr ($p < 0.001$ and $p = 0.004$) Fatal bleeding: 0.1% and 0.2%/yr vs. 0.4%/yr ($p < 0.001$ and $p = 0.006$) GI bleeding: 0.8% and 1.5%/yr vs. 1.2%/yr ($p < 0.001$ and $p = 0.03$)

*Patients enrolled in study (randomization was carried over from RE-LY); RELY-ABLE was a descriptive study with no formal primary endpoints. †Half dose in patients with CrCl 30 to 50 ml/min, body weight ≤60 kg, or receiving verapamil, quinidine, or dronedarone.
ASA = acetylsalicylic acid; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack (2 points); GI = gastrointestinal; ICH = intracranial hemorrhage; RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy; RELY-ABLE = Long Term Multi-Center Extension of Dabigatran Treatment with Atrial Fibrillation; other abbreviations as in Tables 1 and 3.

bid rivaroxaban dose was associated with a lower risk of bleeding compared with the higher (5 mg bid) dose (0.1% vs. 0.4%; $p = 0.04$). The U.S. Food and Drug Administration has not approved rivaroxaban use in patients with ACS.

EDOXABAN. Edoxaban is a direct factor Xa inhibitor that is not currently licensed in Europe or the United States (Table 1). Edoxaban was compared with LMWH/warfarin for the treatment of VTE in the randomized phase III Hokusai-VTE study (8). Patients in both treatment arms received heparin induction at the start of treatment. Edoxaban was noninferior to warfarin for the prevention of recurrent symptomatic VTE and led to a significantly lower incidence of major plus nonmajor clinically relevant bleeding ($p = 0.004$) (Table 3) (8). There was a similar incidence of major bleeding in both treatment arms (1.4% vs. 1.6%; $p = 0.35$), and fatal bleeding occurred in 2 patients in the edoxaban arm compared with 10 in the warfarin arm. There were no fatal intracranial or retroperitoneal bleeding events with edoxaban, and fewer nonfatal bleeding episodes in a critical site compared with warfarin (0.3% vs. 0.6%, including 5 vs. 12 nonfatal ICHs) (8).

The efficacy and safety of edoxaban for the prevention of stroke in patients with nonvalvular AF was evaluated in the Engage AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) study (Table 5) (7). Edoxaban was noninferior to warfarin for the incidence of stroke and systemic embolism. Major bleeding occurred with a significantly lower incidence with both edoxaban doses compared with warfarin (1.6% and 2.8%/year, respectively, vs. 3.4%/year; $p < 0.001$ for both doses) (Table 5) (7). The endpoint of death or ICH also occurred in significantly fewer patients receiving edoxaban than warfarin (4.0% and 4.3%/year, respectively, vs. 4.9%/year; $p < 0.001$ and $p = 0.004$, respectively). Of note, fatal bleeding (0.1% and 0.2%/year vs. 0.4%/year; $p < 0.001$ and $p = 0.006$, respectively) and life-threatening bleeding (0.3% and 0.4%/year vs. 0.8%/year; $p < 0.001$ for both doses) were significantly less frequent with edoxaban, as was gastrointestinal bleeding with the lower dose (0.8% vs. 1.2%/year; $p < 0.001$). In contrast, the higher edoxaban dose led to more gastrointestinal bleeding than warfarin (1.5% vs. 1.2%/year; $p = 0.03$) (7).

DABIGATRAN. Dabigatran is a direct factor IIa (thrombin) inhibitor and is approved in Europe for thromboprophylaxis in patients undergoing total hip and knee replacement, in the United States for VTE treatment, and in Europe and North America for the

prevention of stroke and systemic embolism in patients with nonvalvular AF (**Table 1**) (5,6).

RE-NOVATE (Dabigatran Etexilate in Extended Venous Thromboembolism [VTE] Prevention After Hip Replacement Surgery) and RE-NOVATE II (Dabigatran Etexilate Compared With Enoxaparin in Prevention of Venous Thromboembolism [VTE] Following Total Hip Arthroplasty) were noninferiority studies comparing dabigatran 150 mg or 220 mg qd (starting with a half-dose 1 to 4 h after surgery) with enoxaparin 40 mg qd (initiated before surgery) for VTE prophylaxis in patients undergoing total hip replacement (34,35). The same doses were also studied after knee replacement surgery in the RE-MODEL (Dabigatran Etexilate 150 mg or 220 mg Once Daily (o.d.) Versus (v.s.) Enoxaparin 40 mg o.d. for Prevention of Thrombosis After Knee Surgery) (vs. enoxaparin 40 mg qd) and the RE-MOBILIZE (vs. enoxaparin 30 mg bid) (36,37). In these studies, the rates of major bleeding were similar (**Table 2**) (34–37).

Dabigatran was studied for acute treatment of VTE in the RE-COVER (Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism) and the RE-COVER II (Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp Venous Thromboembolism [VTE]) (38,39). All patients received initial parenteral anticoagulation. In both trials, dabigatran was noninferior to standard care, and there was no significant difference in the incidence of major bleeding (**Table 3**) (38,39). In the RE-COVER, there were no cases of ICH with dabigatran, but approximately one-fourth of all bleeding events with dabigatran were gastrointestinal. Two further studies considered the potential role of dabigatran as a long-term therapy for the prevention of recurrent VTE after patients had received initial treatment for a primary event. Dabigatran was noninferior to warfarin (RE-MEDY [Secondary Prevention of Venous Thrombo Embolism (VTE)]) and superior to placebo (RE-SONATE [Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE]) for the prevention of recurrent VTE (40). Only 2 major bleeding events occurred with dabigatran in the RE-SONATE (**Table 4**), and there were numerically fewer incidences of major bleeding with dabigatran than with warfarin in the RE-MEDY, including major bleeding in a critical organ, causing a decrease in hemoglobin, or requiring a blood transfusion. However, there was a greater incidence of ACS in patients taking dabigatran than in those receiving warfarin (0.9% vs. 0.2%; $p = 0.02$).

The profile of long-term dabigatran therapy has been further defined by the RE-LY (Randomized Evaluation of Long term anticoagulant therapY) study (**Table 5**), in which 110-mg and 150-mg bid doses were compared with standard warfarin therapy for the prevention of stroke and systemic embolism in patients with nonvalvular AF (41). The lower dabigatran dose was noninferior for efficacy to warfarin in this trial, and the higher dose was superior. The 110-mg dose of dabigatran conferred a significantly lower rate of major bleeding, and the 150-mg dose had a similar rate of major bleeding compared with warfarin (2.7% vs. 3.1% vs. 3.4%/year; $p = 0.003$ and $p = 0.31$, respectively). Both doses significantly reduced intracranial and life-threatening bleeding, but the higher dabigatran dose was associated with a higher rate of gastrointestinal bleeding (**Table 5**) and a slight increase in the rate of myocardial infarction compared with warfarin (41). In the RELY-ABLE (Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) extension study, patients randomized to dabigatran in the RE-LY who had not permanently discontinued treatment continued to receive dabigatran. Rates of major bleeding remained similar to those in the RE-LY, with the lower dose associated with a significantly lower risk than the higher dose (3.7% vs. 3.0%/year, respectively; hazard ratio: 1.26; 95% confidence interval: 1.04 to 1.53). There was no significant difference between the doses in the risk of life-threatening, fatal, gastrointestinal, or intracranial bleeding (**Table 5**) (42).

BLEEDING RISK IN PATIENTS TREATED WITH DOACS

Based on data from phase III studies, DOACs can be expected to have a risk of clinically relevant bleeding similar to that with standard anticoagulants. The rate of major bleeding is also generally similar; however, in clinical trials of apixaban for VTE treatment and rivaroxaban for PE treatment, significant (69% and 51%) relative risk reductions in major bleeding compared with standard therapy have been demonstrated (18,31). When used for extended periods for the prevention of stroke, the DOACs were also associated with clinically important reductions in major bleeding compared with warfarin, including life-threatening bleeding types (7,21,32,41). An ~50% reduction in ICH, a major complication associated with long-term warfarin use (43), is notable. This may be related to lower suppression of thrombin generation with DOACs compared with warfarin (44) and possibly tissue factor-dependent mechanisms. However, there may also be an increase in other types of

bleeding compared with warfarin, such as gastrointestinal hemorrhage (7,32,38,41).

Certain patient groups are at increased risk of bleeding and therefore require careful assessment of the benefit-risk balance of anticoagulant treatment, particularly when continued long term. When bleeding occurs in patients treated with a DOAC, knowledge of the pharmacokinetic and pharmacodynamic characteristics of the agent concerned is important to inform clinical management. Apixaban, rivaroxaban, edoxaban, and dabigatran all reach maximal concentrations between 1 and 4 h after intake and have relatively short half-lives, ranging from 5 to 17 h in healthy subjects (1–6,45) (**Table 1**), which contrasts with the long half-life of warfarin (~40 h) (46). However, drug elimination may be prolonged owing to specific factors, the most important of which are the renal clearance profiles of the patient and the drug. Dabigatran is mostly removed by the kidneys (~80% of a dose is recoverable as unchanged drug in the urine) (47) and may therefore accumulate in patients with renal insufficiency, whereas rivaroxaban (48,49) and apixaban (50) are less affected to a clinically relevant degree by moderate renal impairment (creatinine clearance [CrCl] 30 to 49 ml/min): ~33% of rivaroxaban is cleared as active drug by renal mechanisms (3,4); 25% to 28% of apixaban is cleared by renal elimination (**Table 1**) (1,2). Severe renal impairment (CrCl, 15 to 29 ml/min) leads to a doubling of the half-life of dabigatran (51). Edoxaban has an intermediate profile, with 50% of the dose undergoing renal elimination (52).

Patients with moderate renal impairment (CrCl, 30 to 49 ml/min) who are receiving rivaroxaban for VTE treatment do not require dose adjustment, although in Europe, a 15-mg qd dose after the initial 3 weeks of 15-mg bid dosing may be considered based on clinical evaluation of the risk of thrombosis and bleeding (3). In contrast, patients with AF and moderate renal impairment who receive rivaroxaban for stroke prevention should always receive a 15-mg qd dose (**Table 1**). In Europe, caution is recommended in all patients who have severe renal insufficiency (CrCl, 15 to 29 ml/min); in the United States, rivaroxaban is not recommended in these patients (3,4). Apixaban is given at a reduced dose for the prevention of stroke in some patients with AF (**Table 1**) (1,2). Dose reduction with dabigatran for patients with AF should also be considered in patients with renal impairment and those receiving comedications with interaction potential (**Table 1**). Dabigatran is contraindicated in patients with CrCl 15 to 29 ml/min in Europe but may be used with caution in these patients in the United States at a reduced dose (5,6). No DOAC should be used in patients with CrCl <15 ml/min. Recommendations for edoxaban, if and when approved in North America or Europe, remain to be determined, but a dose reduction was mandated in the Hokusai-VTE and Engage AF-TIMI 48 studies for certain patients (**Table 1**) (7,8).

Hepatic impairment also increases the risk of bleeding. Moderate hepatic impairment (Child-Pugh B) affects the pharmacokinetics of rivaroxaban and apixaban (but not dabigatran) to a clinically relevant degree (1,2,53,54), and severe hepatic impairment would be expected to lead to a substantial increase in bleeding risk with any anticoagulant. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child-Pugh B or C (3,4). Apixaban can be used with caution in patients with Child-Pugh B (1,2), whereas any liver impairment expected to affect survival is a contraindication to dabigatran (5,6). In Japan, caution is advised when using edoxaban in patients with severe hepatic impairment (55).

Interactions with concomitant drugs that share the elimination pathways of an anticoagulant may also serve to increase exposure and thus trigger a bleeding episode. The DOACs have a considerably lower potential for drug-drug interactions than VKAs (9), but there are relevant interactions (**Figure 1**). Apixaban and rivaroxaban are metabolized mainly via cytochrome P450 (CYP) 3A4-dependent and P-glycoprotein (P-gp)-dependent pathways (1,2,49), and bleeding may be caused by the use of comedications that interact strongly with both these pathways. This is of greatest clinical relevance with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole) and human immunodeficiency virus protease inhibitors (e.g., ritonavir) (49), and apixaban (1,2) and rivaroxaban (3,4) should not be coadministered with these drugs (**Table 1**). Strong inhibitors of 1 pathway or moderate inhibitors of both had a lesser effect that was not considered clinically relevant (1,2,49), but concomitant use in patients with renal impairment could still lead to relevant pharmacodynamic effects. Strong CYP3A4 inducers should also be used with caution or avoided with rivaroxaban and apixaban. In contrast, neither dabigatran nor its prodrug, dabigatran etexilate, is metabolized by CYP-dependent mechanisms (5,6). However, both are P-gp substrates (5,6), and the effect of strong P-gp inhibitors on the bioavailability of dabigatran could be greater than with rivaroxaban and apixaban. Less than 4% of an edoxaban dose is subject to CYP3A4-dependent clearance, which may allow use in patients taking concomitant medications that would preclude use of rivaroxaban or apixaban (52).

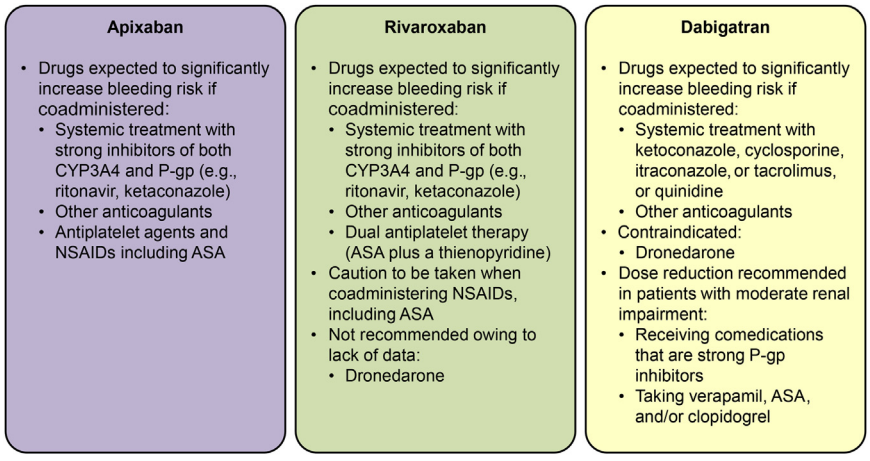

FIGURE 1 Clinically Relevant Drug Interactions That May Increase Bleeding Risk With the Approved Direct Oral Anticoagulants (1–6)

Recommendations are not currently available for edoxaban because it is not yet licensed in Europe or North America. Moderate renal impairment defined as creatinine clearance 30 to 49 ml/min. ASA = acetylsalicylic acid; CYP3A4 = cytochrome P450 3A4; NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein.

Unlike with VKAs, food interactions with DOACs are minimal and not likely to cause overexposure. Rivaroxaban doses of 15 mg and 20 mg should be taken with food (**Table 1**) (56,57). There was a modest effect on the pharmacokinetic parameters of edoxaban when taken with food, but this is not expected to be of clinical relevance (58).

In patients with AF who are receiving long-term anticoagulation therapy for stroke prevention, ACS or VTE may develop, the latter perhaps owing to poor warfarin control. For the former, unless the event is immediately life-threatening (e.g., massive PE requiring thrombolysis or embolectomy), such patients can be transitioned to rivaroxaban (as the only DOAC approved for VTE treatment in the European Union and the United States) at the initial 15-mg bid dose (3,4). During the initial 3-week 15-mg bid dosing period with rivaroxaban, patients should be monitored closely for signs of bleeding, although in the EINSTEIN DVT and EINSTEIN PE trials, there was no increase in major bleeding compared with enoxaparin/VKA during this phase (30,31). If rivaroxaban is used in patients taking antiplatelet agents for AF, an increase in bleeding risk is likely; this may be particularly important because patients with AF are generally elderly and may have renal impairment or other comorbidities and/or be taking medications that interact with rivaroxaban to increase exposure. If the benefit-risk profile is favorable, rivaroxaban may be combined with doses of ASA not exceeding 100 mg/day (59), but dual-antiplatelet therapy should not be combined with rivaroxaban in patients with AF. In contrast, a low dose of rivaroxaban may now be combined with single- or dual-antiplatelet therapy in Europe for patients with recent ACS, if they have elevated cardiac biomarkers indicating a likely secondary event (3). The approved dose of rivaroxaban (2.5 mg bid) in ACS is much lower than that in other indications. In patients without elevated biomarkers, the addition of anticoagulation to antiplatelet treatment cannot be justified because of the significant increase in risk of major bleeding, as observed in the APPRAISE-2 (22) and ATLAS ACS 2 TIMI 51 (33) trials. Rivaroxaban is not approved for patients with both AF and ACS.

MONITORING ANTICOAGULATION WITH THE DOACS

Routine coagulation monitoring is not required with DOACs but is recommended in patients with renal impairment, acute bleeding, overdoses, or emergency surgery (10). The interval between the last dose and sampling must be considered when interpreting the test results. Rivaroxaban prolongs the prothrombin time (PT), with substantial interassay variability (60). The PT provides a qualitative indication of the anticoagulant effect but does not measure drug levels. The international normalized ratio (INR) should not be used for rivaroxaban (60) or for other direct factor Xa inhibitors (61). Specific anti-factor Xa assays, distinct from LMWH testing, are recommended for

TABLE 6 Appropriateness of Assays for Monitoring the Activity of Direct Oral Anticoagulants (60,61,63)

Drug	Quantitative Assays (Provides an Estimate of Anticoagulant Drug Levels)	Qualitative Assays (to Indicate Presence or Absence of Drug Effect)	Not Recommended
Direct factor Xa inhibitors (apixaban/rivaroxaban/edoxaban)	Specific, calibrated anti-factor Xa assays	Prothrombin time assay read in seconds with sensitive reagents	Insensitive prothrombin time, activated partial thromboplastin time, thrombin inhibition, or heparin-specific assays
Direct thrombin inhibitor (dabigatran)	HEMOCLOT (Aniara, West Chester, Ohio) dilute thrombin assay	Activated partial thromboplastin time, ecarin clotting time, thrombin time	Assays that do not measure thrombin inhibition, heparin-specific assays

quantitative measurements of rivaroxaban, apixaban, and likely for edoxaban (**Table 6**) (60,61).

Dabigatran prolongs most coagulation assays except PT (62). A normal thrombin time assay can be used to exclude a clinically relevant dabigatran effect and is better for this purpose than the activated partial thromboplastin time, although the dilute thrombin time assay HEMOCLOT (Aniara, West Chester, Ohio) better correlates with plasma concentrations and is more sensitive for dabigatran (**Table 6**) (63). The ecarin clotting time test provides a dose-dependent correlation with dabigatran (64) but is not widely available.

PERI-PROCEDURAL MANAGEMENT

DOACs have a faster onset/offset of action than VKAs and can theoretically be stopped closer to the time of surgery (10). Rivaroxaban can be stopped up to 24 h before based on European and U.S. prescribing recommendations (3,4). A general principle is that pre-procedural DOAC discontinuation should be based on the specific pharmacokinetics, renal function, and procedural bleeding risk; post-procedural DOAC resumption should be based on bleeding risk and whether adequate hemostasis has been achieved (65).

Recommendations suggest stopping DOACs ~24 h (2 to 3 half-lives) before a procedure that carries a low bleeding risk, but 5 days before with a medium or high bleeding risk, dependent on the DOAC and the patient's renal function (66,67). The European Heart Rhythm Association suggests stopping DOACs ≥24 h before surgery for low-risk procedures and ≥48 h before high-risk surgery, but longer for patients with CrCl <80 ml/min for dabigatran and CrCl 15 to 30 ml/min for rivaroxaban or apixaban (68). Other expert consensus documents recommend 24- to 48-h discontinuation windows (65). Using such a scheme in the RE-LY trial yielded similar rates of peri-operative bleeding/thromboembolism in

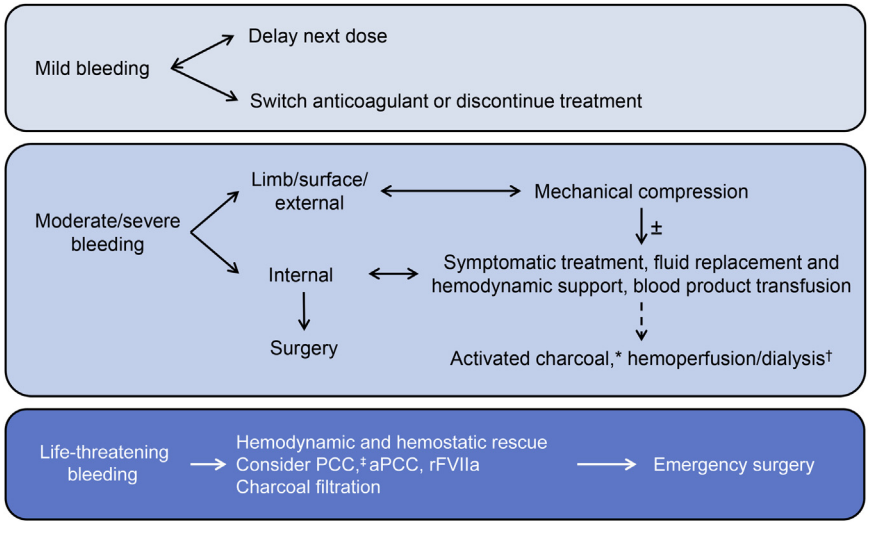

FIGURE 2 Suggested Algorithm for Bleeding Management in Patients Receiving Direct Oral Anticoagulants

*If the anticoagulant was taken within 6 h of admission. †Dabigatran only. ‡3- and 4-component PCCs are available; it is not clear which is preferred. aPCC = activated prothrombin complex concentrate; PCC = prothrombin complex concentrate; rFVIIa = recombinant factor VIIa.

TABLE 7 Ongoing Clinical Studies of Direct Oral Anticoagulants in Thromboembolic and Cardiovascular Conditions

Study Name/Clinicaltrials.gov Identifier	Study Type/Design	Patients (Number Randomized)	Study Objectives	Study Duration	Status
COMPASS/NCT01776424	Phase III, multicenter, randomized, double-blind, active-control, superiority	Age ≥18 yrs diagnosed with CAD or PAD (N = 19,500)	To evaluate rivaroxaban and ASA or rivaroxaban alone compared with ASA alone for prevention of myocardial infarction, stroke, or cardiovascular death	Feb 2013–Feb 2018	Ongoing (recruiting)
ePAD/NCT01802775	Phase II, multicenter, randomized, open-label, parallel-group, active-control	Age ≥18 yrs with PAD (N = 200)	To assess the safety and potential efficacy of edoxaban plus ASA after femoropopliteal endovascular intervention, with or without stent placement, relative to the standard care of clopidogrel plus ASA	Jan 2013–Jun 2014	Ongoing (recruiting)
ADANCE/NCT01924325	Phase II/III, multicenter, randomized, double-blind, active-control, superiority	Age ≥18 yrs with acute nondisabling cerebrovascular event (N = 10,000)	To assess whether 21 days of apixaban is superior to clopidogrel and ASA dual therapy	Jan 2014–Jul 2016	Ongoing (not yet recruiting)
COMMANDER HF/ NCT01877915	Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled event-driven	Age ≥18 yrs with chronic heart failure and significant CAD (N = 5,000)	To assess the effectiveness and safety of rivaroxaban compared with placebo in reducing the risk of death, myocardial infarction, or stroke after a recent hospitalization for exacerbation of heart failure	Sep 2013–Feb 2016	Ongoing (recruiting)
X-PLORER/NCT01442792	Phase II, multicenter, randomized, semiblinded, active-control	Age ≥18 yrs with symptomatic CAD and due to undergo elective PCI (N = 108)	To assess the efficacy and safety of rivaroxaban compared with unfractionated heparin, both with standard dual-antiplatelet therapy for suppression of thrombosis and related adverse ischemic events, upon balloon inflation and stent expansion, during elective PCI	Oct 2011–Mar 2013	Completed
PIONEER AF-PCI/ NCT01830543	Phase III, multicenter, randomized, open-label, active-control	Age ≥18 yrs with paroxysmal, persistent, or permanent nonvalvular AF and who have had PCI with stent placement (N = 2,169)	To evaluate the safety of 2 different rivaroxaban treatment strategies and 1 VKA treatment strategy with various combinations of dual-antiplatelet or low-dose ASA or clopidogrel (or prasugrel or ticagrelor)	May 2013–Mar 2016	Ongoing (recruiting)
X-TRA/NCT01839357	Phase III, multicenter, open-label, single-group	Age ≥18 yrs diagnosed with nonvalvular AF or atrial flutter with left atrial or left atrial appendage thrombus (N = 60)	To explore the efficacy of rivaroxaban for the treatment of thrombi. The study will measure thrombus outcomes based on echocardiographic image and common clinical outcomes such as bleeding and stroke or thromboembolism	Aug 2013–May 2015	Ongoing (recruiting)
ARTESiA/NCT01938248	Phase IV, randomized, double-blind, parallel-group, active-control	Patients with subclinical AF and additional stroke risk factors who have a pacemaker or implantable defibrillator (N = 4,000)	To compare the efficacy and safety of apixaban with that of ASA for the prevention of ischemic stroke and systemic embolism	Dec 2013–May 2018	Ongoing (not recruiting)
BRUISECONTROL2/ NCT01675076	Phase III, randomized, prospective, open-label	Patients with AF at moderate to high risk of stroke scheduled for device surgery (N = 846)	To determine the best strategy to manage dabigatran at the time of pacemaker or defibrillator surgery, with the hypothesis that performing device surgery without interruption of dabigatran will result in a reduced rate of clinically significant hematoma	Jan 2013–Jun 2015	Ongoing (recruiting)
VENTURE-AF/ NCT01729871	Phase III, multicenter, randomized, open-label, parallel-group, active-control	Age ≥18 yrs diagnosed with nonvalvular AF undergoing catheter ablation (N = 200)	To evaluate the safety of rivaroxaban and VKA as measured by post-procedure major bleeding events	Feb 2013–Sep 2014	Ongoing (recruiting)
DAPPAR AF/ NCT01468155	Phase IV, open-label, single-group	Age ≥18 yrs diagnosed with symptomatic, paroxysmal or persistent AF undergoing catheter ablation (N = 200)	To investigate whether peri-ablation with dabigatran is a safe and effective method of periprocedural anticoagulation	Nov 2011–Jul 2014	Ongoing (recruiting)
ODIn-AF/NCT02067182	Phase IV, randomized, open-label, parallel-group, superiority	Age ≥18 yrs with asymptomatic AF at high continuing stroke risk after successful ablation (N = 630)	To determine whether continued administration of dabigatran is superior in the prevention of silent cerebral embolism to discontinuation of oral anticoagulant after 3 months	Oct 2014–Jun 2016	Ongoing (not recruiting)

Continued on the next page

TABLE 7 Continued

Study Name/Clinicaltrials.gov Identifier	Study Type/Design	Patients (Number Randomized)	Study Objectives	Study Duration	Status
X-VERT/NCT01674647	Phase III, multicenter, randomized, open-label, parallel-group, active-controlled, prospective	Age ≥18 yrs with nonvalvular AF scheduled for cardioversion (N = 1,504)	To explore the efficacy and safety of rivaroxaban compared with dose-adjusted VKAs for the prevention of cardiovascular events in patients with nonvalvular AF scheduled for cardioversion	Oct 2012–Jan 2014	Completed
EMANATE/NCT02100228	Phase IV, randomized, open-label, active-control	Age ≥18 yrs with nonvalvular AF indicated for cardioversion and initiation of anticoagulation (N = 1,500)	To assess the efficacy and safety of apixaban compared with that of warfarin for patients in whom an early cardioversion is planned	Jun 2014–Jan 2016	Ongoing (not recruiting)
ENSURE-AF/NCT02072434	Phase III, multicenter, randomized, open-label, active-control	Age ≥18 yrs with nonvalvular AF scheduled for cardioversion (N = 2,200)	To compare the efficacy and safety of edoxaban with warfarin and enoxaparin for patients undergoing cardioversion	Mar 2014–Jul 2015	Ongoing (recruiting)
NCT01493557	Phase IV, multicenter, randomized, open-label, parallel-group	Age ≥18 yrs with nonvalvular AF not previously treated with dabigatran (N = 1,200)	To evaluate the efficacy of 2 management strategies of GI symptoms in patients newly on treatment with dabigatran for the prevention of stroke and systemic embolism	Dec 2011–Jul 2014	Ongoing (not recruiting)
NCT02022020	Retrospective, observational, cohort	Age ≥18 yrs with confirmed diagnosis of nonvalvular AF (N = 200)	To assess the management of GI and urogenital bleeding events in patients treated with dabigatran	Jan 2014–May 2014	Ongoing (recruiting)
NCT01896297	Phase IV, prospective, open-label, single-group	Age ≥18 yrs with confirmed diagnosis of nonvalvular AF and severe renal impairment (N = 75)	To evaluate the pharmacokinetics of dabigatran oral 75 mg bid in these patients	Jul 2013–Aug 2014	Ongoing (recruiting)
XANTUS/NCT01606995	Multicenter, observational, prospective, cohort	Age ≥18 yrs with nonvalvular AF (N = 6,000)	To observe outcomes in patients prescribed rivaroxaban under routine treatment conditions to prevent stroke or non-central nervous system systemic embolism	Jun 2012–Jul 2015	Ongoing (not recruiting)
EINSTEIN CHOICE/ NCT02064439	Phase III, multicenter, randomized, double-blind, active-control	Age ≥18 yrs with confirmed symptomatic DVT and/or PE who have received 6–12 months of anticoagulant treatment (N = 2,850)	To compare the efficacy and safety of extended rivaroxaban at the currently approved 20-mg qd dose or a half dose with ASA for prevention of VTE recurrence	Mar 2014–Nov 2016	Ongoing (recruiting)
EINSTEIN JUNIOR/ NCT01684423	Phase II, randomized, open-label, parallel-group, active-control	Age 6–17 yrs with venous thrombosis (N = 50)	To determine the safety, efficacy, and PK/PD of oral rivaroxaban	Feb 2013–Sep 2015	Ongoing (recruiting)
NCT01895777	Phase III, multicenter, randomized, parallel-group, active-control, noninferiority	Age ≤17 yrs with confirmed VTE (N = 270)	To assess the efficacy, safety, and PK of dabigatran versus low molecular weight heparin or VKA and the appropriateness of the proposed dabigatran pediatric dose using 3 different formulations	Sep 2013–Mar 2018	Ongoing (recruiting)
NCT01707394	Phase I, nonrandomized, open-label, parallel-group	Age 37 weeks to <18 yrs at risk of thrombosis (N = 40)	To evaluate the PK, PD, safety, and tolerability of apixaban in children	Jan 2013–May 2015	Ongoing (recruiting)
AVERT/NCT02048865	Phase II, randomized, double-blind, parallel-group, placebo-controlled, superiority	Age ≥18 yrs with cancer (N = 574)	To assess the safety and the superiority of apixaban thromboprophylaxis for patients with cancer	Jan 2014–Jun 2017	Ongoing (recruiting)
NCT02073682	Phase III, active-control	Age ≥18 yrs with cancer and confirmed VTE (number unknown)	To compare edoxaban with dalteparin for prevention of recurrent VTE after an initial index event	To Dec 2017	Ongoing (not recruiting)
XALIA/NCT01619007	Observational, prospective	Age ≥18 yrs with a diagnosis of acute DVT (N = 4,800)	To analyze the long-term safety of rivaroxaban in DVT treatment in routine clinical practice	Jun 2012–Jun 2015	Ongoing (not recruiting)
MARINER/NCT02111564	Phase III, randomized, double-blind, parallel-group, placebo-controlled	Medically ill patients age ≥40 yrs at high risk of VTE (N = 8,000)	To evaluate the efficacy and safety of rivaroxaban compared with placebo in the prevention of symptomatic venous thromboembolic events and VTE-related death after hospital discharge	Apr 2014–Feb 2017	Ongoing (not recruiting)

Correct as of May 2014.

CAD = coronary artery disease; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; other abbreviations as in Tables 1, 3, and 5.

warfarin- and dabigatran-treated patients (69). Additional studies are ongoing (65).

If the patient's risk of thrombosis warrants resumption of anticoagulation after periprocedural cessation, DOAC administration can be resumed 12 to 24 h after procedures associated with rapid and complete restoration of hemostasis. In general, DOACs may be resumed within 24 h for a procedure with a low risk of bleeding, and within 48 to 72 h for a procedure with a high risk of bleeding (65). For procedures associated with an inability to take oral medications (e.g., post-operative intestinal ileus), bridging with either unfractionated heparin or reduced-dose LMWH may be considered before transitioning to a DOAC 48 to 72 h post-surgery (68). Bridging therapy with a DOAC should otherwise be avoided, except in patients with very high thrombotic risk (65).

INTERRUPTION OF DOACS AND SWITCHING BETWEEN ANTICOAGULANTS

In the ROCKET AF study, thromboembolic events increased when patients discontinued rivaroxaban; however, temporary interruption led to low rates of stroke and major bleeding similar to those with warfarin (32,70). Prolonged inadequate anticoagulation should be avoided if a DOAC is discontinued for reasons other than bleeding, and transitioning to another anticoagulant should be considered. If switching to warfarin/VKA, advice differs between Europe and the United States and between the factor Xa inhibitors and dabigatran. For apixaban and rivaroxaban in Europe, concurrent administration of the DOAC and VKA is recommended for at least 2 days and thereafter until the INR is ≥2.0 (tested at the trough DOAC concentration to minimize interference), after which the DOAC can be discontinued (1,3). For dabigatran, a similar approach is recommended, but with at least 2 days of concurrent DOAC and VKA administration for patients with CrCl of 30 to 49 ml/min, and at least 3 days for those with CrCl ≥50 ml/min (to account for the dependence of dabigatran on renal clearance) (5). The U.S. prescribing information suggests a different approach for apixaban and rivaroxaban of discontinuing the DOAC and starting the VKA plus a parenteral anticoagulant as bridging therapy until the INR reaches the therapeutic range (2,4). For dabigatran, the U.S. advice is similar to that given in Europe, but with 3 days of concurrent administration of DOAC and VKA suggested for patients with CrCl ≥50 ml/min, 2 days for those with CrCl of 30 to 50 ml/min, and 1 day in the case of CrCl of 15 to 30 ml/min (6). For transition to a parenteral anticoagulant (e.g., LMWH in the case of a patient with cancer), the advice is simpler and more uniform: start the parenteral agent and discontinue the DOAC when the next dose of DOAC is scheduled (1–6). However, for dabigatran, it may be necessary to wait 24 h before initiating the new anticoagulant in patients with CrCl <30 ml/min (5,6).

RECOMMENDED MANAGEMENT STRATEGIES FOR BLEEDING ASSOCIATED WITH DOACS

For moderate or severe bleeding, standard hemodynamic support measures, such as fluid replacement and blood transfusion, can be applied to patients receiving DOACs as with other anticoagulants (**Figure 2**). These include mechanical compression (e.g., severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, use of blood products (packed red cells, fresh frozen plasma, or platelets), and, depending on laboratory testing and other factors, cryoprecipitate or fibrinogen concentrates (1–6,52). Rivaroxaban, apixaban, and, it is anticipated, edoxaban, have high protein binding; therefore, they are not dialyzable (1,2,52,71), whereas dabigatran can be partially removed by dialysis (51,72). The use of activated charcoal can be considered in the event of an overdose, provided this is within ~6 h of ingestion. If bleeding occurs and cannot be controlled with these measures, interventions may be required. DOACs should be discontinued before a planned intervention, as discussed (3,4), although renal function is important (10), especially for patients at risk of bleeding (66,67). In emergencies, immediate surgery may be required, and clinical judgment must be exercised. Rivaroxaban, although approved for PE therapy, should not be given to patients with hemodynamically unstable PE (3,4).

MANAGEMENT OF LIFE-THREATENING BLEEDING

If bleeding is life-threatening, the off-label therapeutic use of PCC or activated PCC may be considered to attempt to reverse the anticoagulant effect of the DOACs (1–6). However, experience with these therapeutic approaches is limited to preclinical studies, which have shown variable results (73–78), and reversal of anticoagulation in healthy volunteers (79–83), as well as some case reports in patients. One recent study in healthy volunteers found that 3-factor PCC reversed rivaroxaban-induced changes in thrombin generation more than 4-factor PCC (84). With ICH or serious bleeding, recommendations suggest PCC administration at 50 U/kg or activated PCC (anti-inhibitor coagulant complex) at 30 to 50 U/kg

(85), and readministered once if required (85). Hemodialysis guided by measured drug concentrations should be considered for dabigatran.

A specific reversal agent for factor Xa inhibitors (andexanet alfa) is in development. The molecule is a recombinant protein analog of factor Xa that binds to direct factor Xa inhibitors and antithrombin but does not itself have any catalytic activity. In ex vivo and animal studies, andexanet alfa was able to dose-dependently reverse factor Xa inhibition (86). In addition, a potent monoclonal antibody directed against dabigatran, idarucizumab, is now under clinical investigation; the RE-VERSE AD (RE-VERSal Effects of idarucizumab on Active Dabigatran) study (NCT02104947) will evaluates idarucizumab for dabigatran reversal in patients with uncontrolled bleeding or who require emergency surgery (87).

ONGOING CLINICAL STUDIES

Ongoing trials to investigate the use of DOACs in patients with various cardiovascular conditions and undergoing cardiac interventions are summarized in **Table 7**. Additionally, clinical registries, such as GARFIELD (http://www.tri-london.ac.uk/garfield), will provide further information on the real-world use of DOACs.

CONCLUSIONS

DOACs provide important advantages in the short-term prophylaxis of VTE in patients undergoing hip or knee replacement surgery and in the longer term treatment of VTE and prevention of stroke in patients with AF compared with traditional agents, including reductions in dangerous bleeding types. However, they also have different bleeding profiles that require individualized management approaches. Further study and increasing use of apixaban, rivaroxaban, dabigatran, and edoxaban in real-world practice will help to familiarize physicians with best practice in this area. Development of specific measurement techniques and reversal agents will also provide further tools for the management of bleeding.

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