

The Role of Direct Oral Anticoagulants in the Management of Venous Thromboembolism

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in as many as 900,000 people in the United States each year, with up to 100,000 Americans dying as a result.¹ A common complication, VTE is the most preventable cause of death in hospitalized patients.² Once VTE occurs, long-term mortality is poor, with 25% of patients not surviving 7 days and nearly 40% not surviving the first year.³ Furthermore, PE with or without DVT has been found to be an independent predictor of reduced survival compared with DVT alone.³ Among those who do survive, 30% will experience a recurrence of VTE within 10 years.⁴

Historically, the pathogenesis of VTE has been explained with the 3 components of Virchow's triad: hypercoagulability, hemodynamic changes or hemostasis, and endothelial injury or damage.⁵ To address these underlying causes, treatment for VTE relies heavily on the use of anticoagulation therapy and VTE prophylaxis relies on a combination of anticoagulants and nonpharmacologic options. Traditional anticoagulation therapy for VTE involves the use of unfractionated heparin (UFH), low-molecular weight heparin (LMWH), or fondaparinux.⁶⁻⁸ While effective anticoagulants, these agents must be administered subcutaneously or intravenously, and they present significant risks during use, including development of heparin-induced thrombocytopenia and thrombotic thrombocytopenia syndrome.⁶⁻⁸

In 1954, the FDA approved warfarin, a vitamin K antagonist (VKA), for its use in the management of various clotting disorders.⁹ For almost 6 decades, warfarin remained the sole anticoagulant available for outpatient treatment of VTE. Since October 2010, the FDA has approved 5 direct oral anticoagulants (DOACs) for the treatment or prevention of VTE: dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban.¹⁰⁻¹⁴ Compared with warfarin, which inhibits several clotting factors, DOACs inhibit only 1 clotting factor (ie, thrombin or factor Xa) in the coagulation cascade.¹⁵ These agents collectively offer fixed, predictable dosing; reduced need for laboratory monitoring; and minimal drug-food interactions compared with VKA therapy.⁹⁻¹⁴ However, similar to warfarin, bleeding remains a concern with DOACs.⁹⁻¹⁴ In contrast to warfarin, most DOACs lack a reversal antidote; if serious bleeding occurs, only dabigatran has

ABSTRACT

Appropriate treatment of venous thromboembolism (VTE) is critical to minimizing long-term morbidity and mortality. The emergence of direct oral anticoagulants (DOACs) has provided clinicians with expanded therapeutic options for patients with VTE, and as a result, updated practice guidelines released by the American College of Chest Physicians favor DOACs over traditional anticoagulants, such as warfarin. The newest DOAC, betrixaban, received FDA approval in 2017, with an indication for VTE prophylaxis in hospitalized adults. Additionally, results from the XALIA study on the real-world outcomes of rivaroxaban are now available. A reversal agent for dabigatran, idarucizumab, also received FDA approval in 2017, and other reversal agents are in development. This article will provide an overview of current VTE treatment strategies, with an emphasis on the place in therapy of the DOACs.

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an approved antidote (ie, idarucizumab).⁹⁻¹⁴ The DOACs provide new opportunities for the management of VTE, but also present challenges not seen with traditional therapy. Therefore, it is imperative that healthcare practitioners understand the differences among the DOACs, as well as how they compare with warfarin. This article will provide an overview of VTE management, with a focus on the emergence of DOACs in clinical practice.

Nonpharmacologic Management

For patients with prolonged immobility following long-distance travel and surgical procedures, early and frequent mobilization is recommended.¹⁶ The use of graduated elastic compression stockings (GECSSs) apply pressure to the leg to promote blood flow.¹⁷ This, coupled with appropriate leg movement, pushes blood in the lower veins back to the heart, reducing the risk for clotting.¹⁷ Intermittent pneumatic compression (IPC) devices work similarly to compression stockings. These devices use an inflatable sleeve to squeeze blood from the veins to reduce hemostasis in a more active manner than GECSSs.¹⁷ Compression stockings and pneumatic compression devices are frequently used in hospital settings, particularly in patients undergoing surgical procedures. The 2012 American College of Chest Physicians (ACCP) guidelines for VTE prophylaxis recommend the use of these devices as an alternative to or in conjunction with anticoagulation therapy in 3 distinct populations: 1) nonsurgical patients, such as hospitalized medical patients; 2) nonorthopedic surgical patients; and 3) orthopedic surgery patients.¹⁸⁻²⁰ In the presence of contraindications to anticoagulants, including a high bleeding risk, GECSSs and IPC may be the only prophylactic methods.

Inferior vena cava (IVC) filters are an option for patients at significant risk for PE. These filters work by preventing a DVT from traveling to the pulmonary arteries and causing a PE or stroke.²¹ While published guidelines agree that these devices are necessary in the presence of acute VTE in patients with contraindications to or who failed anticoagulation therapy, recommendations on the use of IVC filters in patients without a contraindication are controversial.^{21,22} Clinicians should be aware that treatment guidelines by the ACCP recommend against the use of IVC filters in patients with VTE treated with anticoagulation.²³ Seeking to resolve uncertainty in the medical community regarding the safety of IVC filters, a recent meta-analysis retrieved 1986 studies, of which 11 met inclusion criteria.²⁴ Researchers found that although IVC filters reduce the risk of subsequent PE (odds ratio [OR], 0.50; 95% CI, 0.33-0.75), they increase the risk for DVT (OR, 1.70; 95% CI, 1.17-2.48), and have no impact on PE-related or all-cause mortality (PE-related mortality: OR, 0.51; 95% CI, 0.25-1.05; all-cause mortality: OR, 0.91; 95% CI, 0.70-1.19).²⁴

Additional procedural options include mechanical thrombectomy or pharmacologic thrombolysis to try to dissolve the clot, indicated mainly in the most severe forms or iliofemoral location of DVT.²⁵

Surgical thrombectomy is rarely indicated today in limb-threatening DVT. Thrombolytic therapy may be delivered through systemic therapy (mainly in PE) or by use of catheter-directed thrombolysis in DVT.²⁶ These procedures carry significant risk for the patient, but may improve mortality and/or quality of life in patients with PE or DVT.²⁶ Additionally, these procedures can help to prevent occurrence of postthrombotic syndrome and chronic thromboembolic pulmonary hypertension, both of which have been associated with poor quality of life.^{27,28} The ACCP guidelines recommend thrombolytic therapy for patients with PE associated with hypotension (grade 2B).²³

Despite the potential benefits, health practitioners should be aware of the risks associated with thrombolytic therapy. A meta-analysis evaluating outcomes with the use of thrombolytic therapy compared with traditional anticoagulants (LMWH, VKA, fondaparinux, or UFH) found the use of thrombolytics to be associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32-0.88) and lower risk of recurrent PE (OR, 0.40; 95% CI, 0.22-0.74). However, thrombolytics were also associated with a greater risk of major bleeding (OR, 2.73; 95% CI, 1.91-3.91) and greater risk of intracranial hemorrhage (OR, 4.63; 95% CI, 1.78-12.04).²⁵

Pharmacologic Management

Outcome goals in patients with PE treated with thrombolytic therapy include reducing thromboembolic burden, pulmonary vascular resistance, and right ventricular dysfunction while more rapidly restoring pulmonary capillary blood flow and effective gas exchange compared with anticoagulation alone.²⁶ In patients with DVT, goals include saving the life, limb, or organ when urgently needed, preventing PE in an acute setting.²⁶ The primary goals of anticoagulant pharmacotherapy in patients with VTE are effective anticoagulation to prevent thrombus extension or embolization to prevent new thrombi from forming and reducing the risk of long-term complications.²⁹ The 2016 ACCP guidelines for antithrombotic therapy in patients with VTE recommend the following:

- In patients with DVT or PE, the panel recommends long-term (3 months) anticoagulant therapy over no such therapy (grade 1B)
- In patients with DVT or PE and no cancer, the panel suggests use of dabigatran, rivaroxaban, apixaban, or edoxaban over VKA therapy (all grade 2B). If the patient cannot be treated with one of these agents, the panel recommends VKA therapy over LMWH (grade 2C)
- In patients with DVT or PE and cancer, the panel suggests LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban (all grade 2C)
- Extended-duration anticoagulant therapy is decided on a case-by-case basis depending on the underlying cause of the VTE and patient history²³

The newest agent, betrixaban, was approved by the FDA on June 23, 2017, for hospital and extended-duration prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other VTE risk factors.¹⁴ Because of its recent approval, betrixaban is not included in the most recent ACCP guidelines. However, it is the only oral anticoagulant indicated for prophylaxis of VTE in adult patients hospitalized for an acute medical illness.³⁰

The mechanisms of action, indications, dosing, important drug-drug interactions, reversal agents, drug-food considerations, and warnings and precautions for the 5 DOACs and warfarin are summarized in [Table 1](#).^{9-14,29}

In treatment of VTE, DOACs offer several advantages over VKA therapy. The anticoagulation effect of a VKA, such as warfarin, is indirect inhibition of vitamin K oxide reductase, resulting in decreased levels of pro-coagulant clotting factors in the direct, indirect, and common pathways. By contrast, DOACs act on the final common pathway of the coagulation cascade.¹⁵ Therefore, DOACs have a more predictable anticoagulant response, fewer drug interactions, and significantly less risk of hemorrhagic stroke compared with warfarin.⁹⁻¹⁴

Except for betrixaban and 15-mg or 20-mg doses of rivaroxaban, which must be taken with food, 10-mg doses of rivaroxaban and the 3 other DOACs may be taken without regard to timing of meals.¹⁰⁻¹⁴ Warfarin has a narrow therapeutic index, which may be affected by other drugs and dietary changes, and must be regularly monitored through use of the international normalized ratio (INR), which is taken daily in early therapy and advances to every 1 to 4 weeks once stable INR is achieved.⁹ The use of INR provides clinicians with a biomarker for current coagulation status⁹; in contrast, DOACs have no monitoring requirements and limited options for drug-specific testing of anticoagulation.²⁹ A single dose of warfarin has a half-life time of approximately 1 week, although the effective half-life time ranges from 20 to 60 hours.⁹ All DOACs boast half-lives of less than 24 hours, although rivaroxaban has the shortest at 5 to 9 hours.¹⁰⁻¹⁴ These shorter half-life times help to compensate for the lack of reversal agent (for all but dabigatran) when bleeding occurs or when surgery is necessary in an acute setting, although the difficulty in determining current coagulation status can be challenging for clinicians. Conversely, the shorter half-life times necessitate stricter adherence compared with warfarin due to more rapid clearance of the drug. Despite these benefits, in patients with severe renal impairment (creatinine clearance less than 15 mL/minute), warfarin remains the drug of choice.²⁹

The ACCP guidelines now recommend the use of DOACs over VKA therapy in most patients. However, choice among DOACs may be challenging for clinicians, as no head-to-head trials have been performed and the guidelines do not recommend any one DOAC over another. Therefore, choosing will depend on individual patient

characteristics. [Table 2](#)^{12,29} provides general guidance for clinicians in choosing among the DOACs.²⁹

Clinical Trials

Phase 3 clinical trials of DOACs have shown similar or superior efficacy to traditional agents in treatment of VTE and, in many cases, improved safety parameters with a decreased risk of bleeding. A review of these pivotal trials is provided below.

Dabigatran

The RE-COVER and RE-COVER II trials evaluated the use of 150-mg dabigatran twice daily versus warfarin in treating acute VTE following therapy with LMWH or UFH for a median of 9 days.³¹ In a pooled analysis of the 2 trials, occurrence of the primary outcome—recurrent VTE or related death during 6 months of treatment—was similar between dabigatran and warfarin (HR, 1.08; 95% CI, 0.64-1.80).³¹ Major bleeding and deaths were similar between the 2 groups; however, the occurrence of any bleeding was lower in the dabigatran group (HR, 0.70; 95% CI, 0.61-0.79).³¹ To build on these pivotal results, a more recent analysis evaluated the net clinical benefit (NCB) from the RE-COVER, RE-COVER II, and RE-MEDY trials.³² When broadly defined to include major bleeding events and clinically relevant nonmajor bleeding events as bleeding outcomes, the NCB of dabigatran was superior compared with warfarin (RE-COVER/RE-COVER II: HR, 0.80; 95% CI, 0.68-0.95; RE-MEDY: HR, 0.73; 95% CI, 0.59-0.91).³² When narrowly defined using only major bleeding events, NCB was similar between dabigatran and warfarin.³²

Rivaroxaban

The efficacy and safety of rivaroxaban in treating VTE were evaluated in the EINSTEIN and EINSTEIN-PE trials.^{33,34} During the EINSTEIN trial, 3449 patients were given either rivaroxaban (dosed 15 mg twice daily for 3 weeks followed by 20 mg once daily) or standard therapy (defined as enoxaparin followed by a VKA).³³ Rivaroxaban had noninferior efficacy to standard therapy regarding the primary outcome of recurrent VTE (HR, 0.68; 95% CI, 0.44-1.04; $P < .001$), and major bleeding or clinically relevant nonmajor bleeding occurred in 8.1% of patients in each group.³³ In a continued-treatment study, rivaroxaban 20 mg daily demonstrated superior efficacy to placebo (HR, 0.18; 95% CI, 0.09-0.39; $P < .001$).³³ The EINSTEIN-PE trial evaluated the same dose of rivaroxaban and outcomes in 4832 patients who had acute symptomatic PE with or without DVT.³⁴ Rivaroxaban was noninferior to standard therapy for the primary efficacy outcome (HR, 1.12; 95% CI, 0.75-1.68).³⁴ The principal safety outcome of major bleeding or clinically relevant nonmajor bleeding occurred in 10.3% of patients taking rivaroxaban and 11.4% of patients on standard therapy (HR, 0.90; 95% CI, 0.76-1.07; $P = .23$); however, major bleeding was observed less often in the rivaroxaban group than the standard therapy group (HR, 0.49; 95% CI, 0.31-0.79; $P = .003$).³⁴

TABLE 1. Comparison of DOACs and Warfarin for the Treatment and Prevention of DVT/PE^{9-14,29}

Agent	MOA Inhibits	Indication	Dosing	Drug-Drug Interactions
Warfarin (Coumadin)	Vitamin K ₁ leading to inhibition of factors II, VI, IX, and X, as well as proteins C and S	VTE, PE, and TE complications with AF and/or cardiac valve replacement. Following MI, reduces risk of mortality, recurrent MI, and TE (eg, stroke)	Tablets: 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg Initial dose is usually 2 to 5 mg once daily, with modifications based on INR monitoring and target goal.	Antibiotics, antifungals, botanical (herbal) products, and inhibitors/inducers of CYP2C9, 1A2, or 3A4
Dabigatran (Pradaxa)	Thrombin	Reduces risk of TE in NVAf, DVT/PE prophylaxis following THA, and treatment of DVT/PE	Capsules: 75, 110, and 150 mg Dosed from 150 to 300 mg daily by indication. Renal adjustment required.	Avoid rifampin. Avoid/dose modify with P-gp inhibitors or inducers with reduced CrCl.
Rivaroxaban (Xarelto)	Factor Xa	Reduces risk of TE in NVAf and treatment of DVT/PE, DVT/PE prophylaxis and treatment, and DVT prophylaxis following THA/TKA	Tablets: 10, 15, and 20 mg Dosed from 10 to 30 mg daily by indication. Renal adjustment required.	Avoid use with combined P-gp and strong CYP3A4 inhibitors or inducers.
Apixaban (Eliquis)	Factor Xa	Reduces risk of TE in NVAf, DVT/PE prophylaxis following THA/TKA, and treatment of DVT/PE	Tablets: 2.5 and 5 mg Dosed from 5 to 20 mg daily by indication	Dual inhibitors of CYP3A4 and P-gp increase levels Dual inducers of CYP3A4 and P-gp reduce levels
Edoxaban (Savaysa)	Factor Xa	Reduces risk of TE in NVAf and treatment of DVT/PE Contraindicated in NVAf when CrCl >95 mL/min	Tablets: 15, 30, and 60 mg Dosed from 30 to 60 mg daily by indication. Renal adjustment required.	Avoid rifampin.
Betrixaban (Bevyxxa)	Factor Xa	Prophylaxis of VTE in adult patients hospitalized for acute medical illness at increased risk	Capsules: 40 and 80 mg Initial dose of 160 mg followed by 80 mg daily. Recommended duration of treatment is 35 to 42 days. Renal adjustment required.	P-gp inhibitors will increase levels.

AF indicates atrial fibrillation; CrCl, creatinine clearance; DVT, deep vein thrombosis; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; MI, myocardial infarction; MOA, mechanism of action; NVAf, nonvalvular atrial fibrillation; PCC, prothrombin complex concentrate; PE, pulmonary embolism; P-gp, P-glycoprotein; TE, thromboembolic event; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism.

Apixaban

The AMPLIFY trial evaluated apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) versus standard therapy (enoxaparin followed by warfarin) in 5395 patients with acute VTE.³⁵ The primary efficacy outcome, recurrent symptomatic VTE or death, occurred in 2.3% of patients in the apixaban group versus 2.7% of patients in the standard therapy group (relative risk [RR], 0.84; 95% CI, 0.60-1.18; $P < .001$ for noninferiority).³⁵ The risk of major bleeding was significantly lower in the apixaban group (0.6% vs 1.8%; RR, 0.31; 95% CI, 0.17-0.55; $P < .001$), and the composite risk of major bleeding and clinically relevant nonmajor bleeding was also significantly lower in the apixaban group (RR, 0.44; 95% CI, 0.36-0.55; $P < .001$).³⁵

Edoxaban

The Hokusai-VTE trial evaluated edoxaban (dosed 60 mg daily or 30 mg daily in patients with impaired kidney function or reduced body

weight) versus warfarin for the treatment of VTE in 4921 patients over 3 to 12 months.³⁶ Regarding the primary efficacy outcome, defined as recurrent symptomatic VTE, edoxaban was found to be noninferior to warfarin (HR, 0.89; 95% CI, 0.70-1.13; $P < .001$ for noninferiority), and major bleeding or clinically relevant nonmajor bleeding occurred significantly less often in the edoxaban group (HR, 0.81; 95% CI, 0.71-0.94; $P = .004$ for superiority).³⁶ In a subgroup analysis of 938 patients with right ventricular dysfunction, recurrent VTE occurred significantly less often in the edoxaban group versus the warfarin group (HR, 0.52; 95% CI, 0.28-0.98).³⁶

Betrixaban

The extended-duration APEX trial evaluated the long-term (up to 42 days) efficacy and safety of 2 doses (40 and 80 mg) of betrixaban compared with enoxaparin for the prevention of VTE in an acutely medically ill hospitalized population with risk factors for VTE.³⁷ By

TABLE 1. (continued) Comparison of DOACs and Warfarin for the Treatment and Prevention of DVT/PE^{9-14,29}

Agent	Reversal Agents	Drug-Food Considerations	Warnings and Precautions
Warfarin (Coumadin)	Vitamin K1, PCC, FFP, or activated factor VII	Diet should remain consistent. Echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort, and foods with vitamin K impact INR.	May cause tissue necrosis, calciphylaxis, acute kidney injury, systemic atheroemboli and cholesterol microemboli, HIT, and harm in pregnant women with mechanical heart valves (benefits outweigh risks). Contraindicated in pregnancy, except in mechanical heart valve.
Dabigatran (Pradaxa)	Idarucizumab. Dialysis may remove; data are limited.	None. May be taken with or without food.	Use not recommended in bioprosthetic heart valves. Risk of bleeding increases with age. Do not use if CrCl <30 mL/min and in mechanical prosthetic heart valves.
Rivaroxaban (Xarelto)	No reversal agent or antidote available. Activated charcoal may help with overdose. Dialysis will not remove.	15 and 20 mg doses must be taken with food. 10 mg dose may be taken with or without food.	Use not recommended in prosthetic heart valves, nursing mothers, or hepatic impairment. Avoid use if CrCl <30 mL/min (VTE indication; in patients with NVAf, may adjust dose as low as 15 CrCl)
Apixaban (Eliquis)	No reversal agent or antidote available. Activated charcoal may help with overdose. Dialysis will not remove.	None. May be taken with or without food.	Use not recommended in prosthetic heart valves, pregnancy, or severe hepatic or renal impairment.
Edoxaban (Savaysa)	No reversal agent or antidote available. Dialysis will not remove.	None. May be taken with or without food.	Reduced efficacy in NVAf with CrCl >95 mL/min. Use not recommended in mechanical heart valves, moderate to severe mitral stenosis, nursing mothers, or hepatic impairment. Do not use if CrCl <15 mL/min.
Betrixaban (Bevyxxa)	No reversal agent or antidote available. There are no data on the ability of dialysis to remove.	Take with food.	Safety in prosthetic heart valves has not been established. Avoid use in hepatic impairment. Use in pregnancy should be with caution. Do not use if CrCl <15 mL/min

study completion, the occurrence of the primary efficacy outcome (DVT event, PE event, or VTE-related death) was significantly reduced among patients receiving 80-mg betrixaban versus 40-mg enoxaparin (4.87% vs 7.06%; RR reduction, 0.30; 95% CI, 0.13-0.44; $P = .001$).³⁷ Efficacy outcomes of patients receiving 40-mg betrixaban did not significantly vary from the outcomes of those receiving enoxaparin, and safety profiles were similar between both doses of betrixaban and enoxaparin.³⁷ Recent data from APEX substudies were presented at the American Heart Association 2017 Scientific Sessions.³⁸⁻⁴⁰ Compared with enoxaparin, betrixaban was associated with a lower disease extent of DVT at 35-42 days ($P = .017$) and reduced VTE-related hospitalizations at 42 days (HR, 0.33; 95% CI, 0.16-0.71; $P = .0027$) and 77 days (HR, 0.44; 95% CI, 0.25-0.80; $P = .0055$).^{38,40} Most importantly, betrixaban demonstrated superiority in reduction of VTE-related death compared with enoxaparin at 77 days (HR, 0.46; 95% CI, 0.22-0.96; $P = .0348$).³⁹

Real-World Comparative Trials

Pivotal phase 3 trials are important for clinicians to understand the performances of these agents in randomized controlled settings, with few confounding variables; however, healthcare practitioners should also be aware of real-world evidence comparing these agents with each other and with VKA therapy regarding efficacy, safety, and adherence rates in clinical practice. Real-world data on the use of these agents in patients with VTE are limited; however, results from the XALIA study are now available.⁴¹ The XALIA study evaluated the effectiveness and safety of rivaroxaban compared with standard therapy (initial treatment with UFH, LMWH, or fondaparinux followed by VKA) in 5142 patients with DVT in hospitals and community care centers across 21 countries.⁴¹ In this real-world setting, the frequency of major bleeding was 0.8% in the rivaroxaban group compared with 2.1% in the standard therapy group (HR, 0.77; 95% CI, 0.40-1.50; $P = .44$), and the frequency of recurrent VTE was

TABLE 2. Choosing Among the DOACs^{12,29}

Characteristics	DOAC Option	Rationale for Selection
CrCl <30 mL/min	Apixaban	Other DOACs are more affected by renal impairment than apixaban
All-oral therapy	Rivaroxaban or apixaban	Dabigatran and edoxaban require UFH or LMWH bridging
Dyspepsia or upper GI complaints	Rivaroxaban, apixaban, or edoxaban	Dyspepsia with dabigatran in up to 10% of patients
Recent GI bleed	Apixaban or low-dose edoxaban	More GI bleeding with rivaroxaban, high-dose dabigatran, or edoxaban
Significant CAD	Rivaroxaban, apixaban, or edoxaban	MI appears to be more common in dabigatran compared with VKA
Poor compliance with twice-daily dosing	Rivaroxaban ^a or edoxaban	Apixaban dosing is twice daily. Dabigatran is twice daily, except in patients receiving VTE prophylaxis following THA (once daily).
Concern regarding reversal agent	Dabigatran (idarucizumab)	No reversal agent is available for DOACs aside from dabigatran

CAD indicates coronary artery disease; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; GI, gastrointestinal; LMWH, low-molecular weight heparin; MI, myocardial infarction; THA, total hip arthroplasty; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aRivaroxaban requires twice-daily dosing during initial 21 days of VTE treatment, then becomes once daily.

1.4% and 2.3%, respectively (HR, 0.91; 95% CI, 0.54-1.54; $P = .72$).⁴¹ Furthermore, the frequency of all-cause mortality was 0.4% in the rivaroxaban group compared with 3.4% in the standard therapy group (HR, 0.51; 95% CI, 0.24-1.07; $P = .074$), and the incidence of treatment-emergent adverse events was similar between the 2 groups.⁴¹ These data demonstrate that the safety and efficacy of rivaroxaban is comparable with standard therapy in a real-world setting; however, additional insight may be gleaned from studies that have compared these agents in patients with nonvalvular atrial fibrillation (NVAF), which are summarized below.

A large US insurance database was used to retrospectively evaluate efficacy and safety outcomes in patients with NVAF who were prescribed dabigatran, rivaroxaban, apixaban, or warfarin.⁴² In comparison with warfarin, the study concluded that for stroke or systemic embolism, apixaban was associated with a significantly lower risk (HR 0.67; 95% CI, 0.46-0.98; $P = .04$) but that dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR, 0.98; 95% CI, 0.76-1.26; $P = .98$; rivaroxaban: HR, 0.93; 95% CI, 0.72-1.19; $P = .56$).⁴² For major bleeding compared with warfarin, apixaban and dabigatran were associated with a significantly lower risk (apixaban: HR, 0.45; 95% CI, 0.34-0.59; $P < .001$; dabigatran: HR, 0.79; 95% CI, 0.67-0.94; $P < .01$), and rivaroxaban was associated with a similar risk (HR, 1.04; 95% CI, 0.90-1.20; $P = .60$).⁴² A recent study by Bala et al queried combined Humana and Medicare databases to compare VTE outcomes following administration of aspirin, warfarin, enoxaparin, or factor Xa inhibitors among patients undergoing total knee arthroplasty (TKA).⁴³ Ninety days after surgery, researchers found that factor Xa inhibitors had

the lowest incidences of DVT and PE ($P < .01$). There were no differences in bleeding-related complications among the groups.⁴³

A study examining adherence rates from a large claims database at 3, 6, and 9 months of follow-up in treatment-naïve patients with NVAF found that dabigatran had the lowest adherence compared with rivaroxaban ($P < .001$) and apixaban ($P < .001$).⁴⁴ Compared with rivaroxaban, patients starting dabigatran had nearly 30% lower odds of being adherent. No differences were observed between apixaban and rivaroxaban groups.⁴⁴ By 9 months, 55% and 56.8% of those taking rivaroxaban and apixaban, respectively, had a proportion of days covered greater than 80%, which was significantly greater than the 46.7% seen with those taking dabigatran ($P < .001$).⁴⁴

Reversal Agents

Although DOACs have demonstrated acceptable safety and efficacy in clinical trials, major bleeding remains a concern, as with any anticoagulant, and in life-threatening bleeding events and emergency situations requiring surgery, a reversal agent can be lifesaving. In recognition of this need, 3 promising agents are approved or in development for reversing the actions of DOACs.

Idarucizumab

Idarucizumab is a humanized murine monoclonal antibody fragment that binds to dabigatran with higher affinity than observed with native thrombin, thereby neutralizing its activity.⁴⁵ An interim analysis of 90 patients in a phase 3 clinical trial found that, among 68 patients with an elevated diluted thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% CI, 100%-100%).⁴⁶ Additionally, idarucizumab normalized the test results in 88% to 98% of the patients, and concentrations of unbound dabigatran remained low after 24 hours in 79% of patients.⁴⁶ Recently published final results from this trial in 503 patients confirmed a dabigatran reversal of 100% (95% CI, 100%-100%), with the median time to cessation of bleeding being 2.5 hours.⁴⁷ Mortality rates were reported as 18.8% and 18.9% in patients who had uncontrolled bleeding or were about to undergo an urgent procedure, respectively, and no serious adverse safety signals occurred during the trial.⁴⁷ Idarucizumab is currently approved for the reversal of dabigatran in emergency surgery, urgent procedures, life-threatening situations, or uncontrolled bleeding.⁴⁵ Adverse events reported in more than 5% of healthy volunteers or patients were headache, hypokalemia, delirium, constipation, pyrexia, and pneumonia.⁴⁵

Andexanet alfa

Andexanet alfa is a recombinant modified human factor Xa decoy protein that binds and thereby reverses the effects of both direct and indirect factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban, low-molecular weight heparin, and fondaparinux).⁴⁸ A multicenter, prospective, open-label, single-group study evaluated 67 patients who had acute major bleeding within 18 hours after the administration of rivaroxaban or apixaban.⁴⁸ After administration of andexanet alfa, the median anti-Xa factor activity decreased by 89% (95% CI, 58%-94%) and 93% (95% CI, 87%-94%) from baseline for patients taking apixaban and rivaroxaban, respectively. These levels remained similar during the 2-hour infusion, and 12 hours after the infusion, clinical hemostasis was adjudicated as excellent or good in 79% (95% CI, 64%-89%) of patients in the efficacy population (n = 47).⁴⁸ Despite these promising results, thrombotic events occurred in 18% of the patients in the safety population (n = 67), and 15% of the patients died during the 30-day follow-up.⁴⁸ A phase 3 trial is ongoing to assess the efficacy and safety of andexanet alfa in patients receiving a factor Xa inhibitor who have an acute major bleed, with expected completion in 2022.⁴⁹

Ciraparantag

Ciraparantag is a small cationic molecule designed to bind all DOACs (both thrombin and Xa inhibitors) and heparins, thereby preventing them from binding to their endogenous targets and reversing their anticoagulant effects.⁵⁰ Promising results from a phase 1 trial in healthy volunteers demonstrated a restoration of baseline homeostasis 10 to 30 minutes after a single dose of 100 to 300 mg of ciraparantag, which was sustained for 24 hours.⁵¹ Phase 2 studies are currently ongoing.^{52,53}

Conclusion

Compared with warfarin, DOACs provide a more predictable anticoagulant response, fewer drug interactions, significantly less risk of hemorrhagic stroke, no monitoring requirements (and therefore fewer office visits), and shorter half-lives. These benefits have catapulted the demand for DOACs ahead of VKA in oral anticoagulation therapy, and clinical guidelines now recommend these agents over warfarin and other standard therapies in most patients requiring VTE prophylaxis and/or treatment.

Even with these benefits, there are many patients in whom DOACs are not suitable. Patients with very poor adherence should receive VKA so they can be appropriately monitored through INR checks, and those who are or may become pregnant should receive LMWHs, as other agents may cross the placenta.²³ Although a reversal agent is now available for dabigatran, the other DOACs lack a specific antidote for reversal in emergency situations. Patients with liver disease, coagulopathy, severe kidney disease, or cancer should not receive DOACs, and clinicians must always remember to consider

cost in the management strategy, as this can impact adherence.²³ Although VTE remains a significant burden to morbidity and mortality for hundreds of thousands of US adults, the emergence of DOACs has given patients and healthcare providers expanded options for anticoagulation therapy. ■

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