DOACs: Oral Anticoagulant Treatment of Choice for Pulmonary Embolism?

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Venous thromboembolism (VTE), which constitutes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality worldwide. There are approximately 900,000 cases of VTE and 60,000 to 100,00 deaths from PE in the United States each year.[1] Anticoagulation is the mainstay of therapy for VTE, and prior to this decade, treatment options were limited to parenteral agents and vitamin K antagonists (VKAs). The emergence of direct oral anticoagulants (DOACs) offers patients a more convenient and accessible alternative. Oral availability, rapid onset, minimal drug interactions, decreased bleeding risk, and comparable efficacy to warfarin/heparin lend agency to the use of DOACs for the treatment of VTE. Presently, dabigatran, rivaroxaban, apixaban, and edoxaban are approved and used routinely for treatment and secondary prevention in patients with DVT and PE. This article focuses on the use of DOACs in patients with PE and highlights the factors involved in deciding on an anticoagulant, different doses and regimens, use in special populations, and recommended duration of anticoagulation.

OVERVIEW OF DOACs

It is well established that early therapeutic anticoagulation improves mortality and decreases acute PE recurrence risk.[2] However, selecting the anticoagulant can be challenging, and the decision depends on factors related to the patient (severity of PE, comorbidities [adequate organ function], bleeding risks, need for invasive procedures, adherence behaviors, preferences, concomitant medications, and weight), anticoagulant (properties of DOACs and potential drug-drug interactions), and clinical judgment. Often, equally important is prescription affordability and insurance coverage.

There are currently four FDA-approved DOACs for the treatment of VTE. Unlike warfarin, DOACs inhibit only one component in the coagulation cascade. Apixaban (Eliquis, Bristol-Myers Squibb Company), rivaroxaban (Xarelto, Janssen Pharmaceuticals, Inc.), and edoxaban (Savaysa, Daiichi Sankyo, Inc.) are factor Xa inhibitors, whereas dabigatran (Pradaxa, Boehringer Ingelheim) is a factor II or direct thrombin inhibitor. The DOACs have several advantages over the older anticoagulants, including a rapid onset of action with predictable pharmacokinetics and pharmacodynamics, fixed dosing, significantly fewer drug and dietary interactions, no discomfort from subcutaneous injections, and no need for routine laboratory monitoring or intravenous access. According to the most recent CHEST guidelines, anticoagulation therapy with one of these four DOACs is suggested over VKAs as long-term therapy in patients with DVT of the leg or PE and no evidence of cancer (grade 2B).[3] This recommendation arose after all four DOACs demonstrated noninferiority to warfarin in preventing recurrent VTE or VTE-related death as well as similar to improved bleeding safety profiles.[4-9]

Currently, there are no head-to-head trials comparing the DOACs. However, because each DOAC has different doses and dosing regimens, it is important for prescribing clinicians to know and understand their nuances (Table 1). For example, rivaroxaban and apixaban are initially given at a higher dose and are approved for the initial therapy of VTE. On the other hand, edoxaban and dabigatran require an initial 5- to 10-day lead-in course of parenteral anticoagulation prior to first dose. Rivaroxaban (after the first 21 days) and edoxaban are taken once daily, whereas apixaban and dabigatran are taken twice daily. Rivaroxaban must be taken with food to maximize oral bioavailability.

The clinical trials evaluating the efficacy of dabigatran, rivaroxaban, apixaban, and edoxaban have convincingly demonstrated the efficacy and safety benefits of these drugs (Table 2).[4-10] Results from meta-analyses pooling data from these trials suggest that DOACs have a similar efficacy (recurrent VTE or death related to VTE) and safety in patients presenting with PE and DVT with a nonsignificant heterogeneity between the groups (risk ratio [RR], 0.90; 95% confidence interval [CI], 0.72–1.13 in PE patients and 0.93; 95% CI, 0.75–1.16 in DVT patients).[11] DOACs reduce the risk of both major and clinically relevant nonmajor bleeding compared to VKAs, with a nonsignificant heterogeneity between the groups (RR, 0.49; 95% CI, 0.26–0.95 in PE patients and 0.74; 95% CI, 0.51–1.06 in DVT patients).[12]

Furthermore, results of randomized clinical trials and meta-analyses indicate that DOACs are as effective as warfarin for VTE treatment (including PE), with lower bleeding risks. The XALIA study is an international, prospective, noninterventional, observational cohort study evaluating the safety and efficacy of rivaroxaban in 5,142 patients with DVT, including patients with concomitant PE.[13] In this real-world study, patients receiving

TABLE 1. PHARMACOKINETIC PROFILES OF DOACs FOR THE TREATMENT AND SECONDARY PREVENTION OF VTE

Key Points	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Mechanism of action	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Direct thrombin inhibitor
Time to peak	2–4 h	3–4 h	1–2 h	1.5 h
Half-life	9–13 h	12 h	10–14 h	12–17 h
Oral bioavailability	66%	> 50%	62%	3%–7%
Excretion	Kidney, 36%; feces, 7%	Kidney, 28.8%; feces, 56%; minimal biliary	Kidney, 50%; rest is biliary/ intestinal and metabolism	Kidney, 80%
Plasma protein binding	92%–95%	~ 90%	55%	35%
Absorption	Primarily proximal small intestine; some gastric absorption	Primarily proximal small intestine; some gastric absorption	Proximal small intestine	Lower stomach and duodenum
Dosing: for initial VTE treatment	15 mg twice daily for 21 d followed by 20 mg daily (with largest meal)	10 mg twice daily for 7 d followed by 5 mg twice daily	Parenteral agent for 5–10 d followed by 60 mg daily or 30 mg daily if any of following: CrCL 15–50 mL/min, weight ≤ 60 kg, or concomitant P-glycoprotein inhibitor	Parenteral agent for 5–10 d followed by 150 mg twice daily
Dosing: for VTE prophylaxis or extended treatment	10 mg daily after at least 6 mo of therapeutic anticoagulation	2.5 mg twice daily after at least 6 mo of therapeutic anticoagulation	Not studied	No dose adjustment
Special considerations	Avoid if CrCL ≤ 30 mL/min or Child-Pugh class B and C; must be taken with food	Avoid if CrCL ≤ 15 mL/ min or Child-Pugh class B and C	Avoid if CrCL ≤ 15 mL/min or Child-Pugh class B and C	Avoid if CrCL ≤ 30 mL/min or Child-Pugh class B and C, if dyspepsia, upper GI symptoms
Dose adjustments*	None (no adjustments for age, weight, or sex)	None (no adjustments for age, weight or sex)	Decrease to 30 mg daily if any of following: CrCl 15–50 mL/min, weight < 60 kg, or concomitant P-glycoprotein inhibitor	None (no adjustments for age, weight, or sex)
Drug interactions	P-glycoprotein, CYP 3A4/5	P-glycoprotein, CYP 3A4/5	P-glycoprotein	P-glycoprotein, PPIs
Laboratory measurement (to determine if present/ not present only)	Anti-Xa	Anti-Xa	Anti-Xa	Dilute thrombin time
Reversal agent	Andexanet (specific) or 4F-PCC (nonspecific)	Andexanet (specific) or 4F-PCC (nonspecific)	4F-PCC (nonspecific)	Idarucizumab (specific)

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; CAD, coronary artery disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; GI, gastrointestinal; PAD, peripheral artery disease; PPI, proton pump inhibitor; VTE, venous thromboembolism.
*No dose adjustments are necessary for the treatment and secondary prevention of VTE. There are different doses and dose adjustments for the use of DOACs in other indications such as prevention of stroke in atrial fibrillation, prevention of VTE in elective hip/knee surgery, and prevention of cardiovascular events with PAD or CAD.

rivaroxaban had a lower risk of major bleeding (hazard ratio [HR], 0.77; 95% CI, 0.40–1.50) and recurrent VTE (HR, 0.91; 95% CI, 0.54–1.54) compared with conventional anticoagulation (initial treatment with unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux followed by a VKA). In all of these trials, the administration of dabigatran or edoxaban was preceded by a course of LMWH or UFH, whereas the remaining DOACs were frequently used from the time of therapy initiation.

INITIAL TREATMENT

After a diagnosis of acute PE and risk stratification for mortality, the treating provider must perform an initial risk/ benefit assessment of anticoagulation, which includes the

TABLE 2. DOAC CLINICAL VTE TRIALS WITH INDEX PE OUTCOMES[4-10]

Trial	Index PE/ Total VTE, n/N (%)	DOAC	Standard AC	Treatment Duration, mo	Primary Efficacy Outcome (Recurrent VTE or VTE-Related Death)		Primary Safety Outcome (Major or NMCR Bleeding)		Safety Outcome (Major Bleeding Episode)	
					DOAC, n/N (%)	Standard AC, n/N (%)	DOAC, n/N (%)	Standard AC, n/N (%)	DOAC, n/N (%)	Standard AC, n/N (%)
RE-COVER and RE-COVER II	1,602/5,107 (31)	UFH or LMWH for ≥ 5 d then dabigatran 150 mg twice daily	UFH or LMWH/VKA	6	23/795 (2.9)	25/807 (3.1)	36/759 (4.7)	55/768 (7.2)	4/759 (0.5)	8/768 (1.0)
EINSTEIN DVT	23/3,447 (< 1)	Rivaroxaban 15 mg twice daily for 21 d followed by 20 mg daily	LMWH/VKA	3, 6, or 12	36/1,731* (2.1)	51/1,718* (3.0)	139/1,718* (8.1)	138/1,711* (8.1)	14/1,718* (0.8)	20/1,711* (1.2)
EINSTEIN PE	4,832/4,832 (100)	Rivaroxaban 15 mg twice daily for 21 d followed by 20 mg daily	LMWH/VKA	3, 6, or 12	50/2,419 (2.1)	44/2,413 (1.8)	249/2,412 (10.3)	274/2,405 (11.4)	26/2,412 (1.1)	52/2,405 (2.2)
AMPLIFY	1,836/5,395 (34)	Apixaban 10 mg twice daily for 7 d followed by 5 mg twice daily	UFH or LMWH/VKA	6	59/2,609* (2.3)	71/2,635* (2.7)	115/2,676* (4.3)	261/2,689* (9.7)	15/2,676* (0.6)	49/2,689* (1.8)
HOKUSAI-VTE	3,319/8,240 (40)	UFH or LMWH for ≥ 5 d then edoxaban 60 mg daily	UFH or LMWH/VKA	3, 6, or 12	47/1,650* (2.8)	65/1,669* (3.9)	349/4,118* (8.5)	423/4,122* (10.3)	56/4,118* (1.4)	66/4,122* (1.6)

Abbreviations: AC, anticoagulant; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; NMCR, nonmajor clinically relevant; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist (goal international normalized ratio, 2.0–3.0); VTE, venous thromboembolism.
*Includes overall VTE study results.

risks of achieving therapeutic anticoagulation balanced by the bleeding risk of the patient on anticoagulation. If the decision is to initiate anticoagulation, a practical approach is to divide treatment into three phases: initial (first 5–10 days and may include parenteral and/or oral anticoagulant), long term (> 10 days to 3–6 months), and extended (> initial 3–6 months). For the acute setting, anticoagulation options include UFH, LMWH, fondaparinux, rivaroxaban, or apixaban. Dabigatran and edoxaban are also effective treatments, but as previously mentioned, both require 5 to 10 days of an initial parenteral anticoagulant and are not approved for stand-alone therapy initially.

With multiple anticoagulant options now available, including the DOACs that do not require an initial parenteral agent, inpatient versus outpatient management of PE has become a part of the initial assessment. Patients with acute PE who are otherwise stable and have no other reason for hospitalization may be considered for outpatient management. Hemodynamic instability (blood pressure < 90 mm Hg, pressor support, or other evidence of shock) is often associated with massive PE, and these patients may be candidates for thrombolytic therapy, whereas hemodynamically stable patients may be considered low risk (small PE, no evidence of right heart strain), in which case systemic anticoagulation is often the only treatment merited. On the other hand, patients with larger PE accompanied by evidence of right heart strain may be candidates for more advanced therapies in addition to systemic anticoagulation. Clearly, the treating physician must consider anticoagulant options in the context of the patient's comorbidities, which include baseline bleeding risk (since this varies with age), renal function, and the type of anticoagulant administered.

EXTENDED TREATMENT

Duration of anticoagulation should be individualized for each patient and should include the initial and periodic

assessment of risk factors for recurrent VTE (transient or persistent) as well as age, sex, obesity, and organ function (liver and kidney). These factors need to be balanced by the risk factors for bleeding on anticoagulation. Overall, this risk/benefit assessment should also include patient preferences (including cost of the anticoagulant). In patients who had a transient risk factor that has resolved, short-term therapy (eg, 3 months) may be reasonable. Alternatively, in patients who had an unprovoked VTE (PE or proximal DVT) or a provoked VTE with ongoing risk factors, long-term anticoagulation may be warranted. All of the DOACs except for edoxaban have been evaluated in randomized trials for extended secondary VTE prevention beyond the initial 3 months. The studies investigating the use of apixaban, rivaroxaban, or dabigatran for secondary prevention of VTE demonstrated superiority in preventing the primary efficacy endpoint of symptomatic recurrent VTE as compared to placebo (AMPLIFY-EXTENSION [apixaban], EINSTEIN-EXTENSION [rivaroxaban], RE-SONATE [dabigatran]) or aspirin (EINSTEIN CHOICE [rivaroxaban]) without a significant increase in major bleeding.[6,14,15] Dabigatran was also found to be noninferior to warfarin in preventing recurrent VTE in an extended VTE prevention trial (RE-MEDY) with significantly lower rates of bleeding.[14] These results support the use of extended duration of anticoagulation in select patients to reduce the lifetime risk of recurrent thrombosis and VTE-associated death.

Importantly, anticoagulation duration should be assessed at least annually, considering risk for VTE recurrence is 7% within the first year and 40% within 5 years.[16] Recent data indicate that long-term nonadherence to DOAC therapy may be as much as 40% to 70% and more severe among patients taking oral medications multiple times each day.[17] Thus, when choosing a DOAC regimen for your patient, all of these issues should be taken into consideration.

All anticoagulants including the DOACs are associated with bleeding, which in rare situations can be life-threatening. Currently, there are two FDA-approved DOAC-specific reversal agents: idarucizumab for dabigatran and andexanet for rivaroxaban and apixaban. Both of these drugs were effective in reversing the anticoagulant effect when administered to patients who presented with serious bleeding.[18,19] Four-factor prothrombin complex concentrate has been used for reversal of anti-Xa DOACs (apixaban, rivaroxaban, edoxaban) prior to andexanet alfa approval or when it is not available. Another reversal agent, ciraparantag, is presently in clinical trials.

SPECIAL POPULATIONS

The choice of DOAC must be made in the context of the specific patient, and DOACs are either contraindicated or have not yet been extensively evaluated in certain patient populations.

Antiphospholipid Syndrome

A history of antiphospholipid syndrome or a clinical presentation consistent with that diagnosis (eg, PE plus arterial thrombosis) should alert the clinician to consider the variance in efficacy of anticoagulants. Available data draw into question whether DOACs are effective or safe in patients with antiphospholipid syndromes. Indeed, apixaban recently updated its labeling to include antiphospholipid syndrome as a warning that DOACs could be associated with increased rates of recurrent VTEs compared to VKA therapy, and DOACs are not recommended in this patient population. Several ongoing trials may settle this issue shortly, but until then, DOACs should probably be avoided in these patients.

Renal Impairment

Use of DOACs in patients with renal impairment is hazardous for several reasons. With the exception of dabigatran, they are not dialyzable and may lead to overaccumulation in patients undergoing dialysis, and in patients with renal failure not on dialysis, bleeding risk increases as renal impairment worsens. In general, all of the DOACs have limited data in patients with significant renal impairment (creatinine clearance ≤ 15–30 mL/min, depending on the DOAC) and are not recommended (Table 1). Although apixaban labeling recommends no dose adjustment for patients with VTE and renal impairment, including those with ESRD on dialysis, this recommendation is based on a very small nonrandomized controlled study (not the clinical efficacy and safety studies that led to its approval) and should be interpreted cautiously. Patients with coronary artery disease and peripheral vascular disease may be candidates for dose-modified rivaroxaban plus antiplatelet therapy. It is important to point out that coronary artery events are more common in patients treated with dabigatran than with a VKA.

Cancer

The treatment of patients with active malignancy and VTE can be challenging. Many patients have an increased risk of bleeding, additive risks of rethrombosis associated with antineoplastic therapy, and a high risk of treatment failure with standard anticoagulation. Present evidence indicates that, at least in the short term, edoxaban and rivaroxaban seem as effective as standard anticoagulation with dalteparin.[20,21] However, both were associated with an increased risk of bleeding in cancer patients when compared to dalteparin.[20,21] Importantly, the bleeding was primarily seen in patients with gastrointestinal cancers. There is an ongoing trial of apixaban in cancer patients. Whether any one of these DOACs is superior to another is uncertain. Given all of these data, clinicians should carefully review the pros (decreased risk of VTE) and cons (increased risk of bleeding) of the use of rivaroxaban and edoxaban in cancer patients with VTE

and make a decision on the type of anticoagulation through shared decision-making.

Pregnancy

No DOACs have been evaluated during pregnancy. There is evidence that they are present in breast milk. Whether this is harmful to the feeding infant is unknown. For this reason, they are best avoided during pregnancy and breastfeeding.

Liver Impairment

Patients with liver impairment should not receive DOACs because the international normalized ratio may be prolonged due to liver synthetic defect during the course of treatment. This will likely increase bleeding risk and confound the use of those DOACs that often prolong the prothrombin time.

Obesity

Few patients with significant obesity have been included in DOAC clinical trials, and their efficacy in relationship to body weight and body fat percentage is unknown. As such, the International Society of Thrombosis and Haemostasis recommends avoiding DOACs in patients > 120 kg or a body mass index > 40 kg/m^2.[22] Similarly, patients < 50 kg were not adequately represented in DOAC clinical trials, so the safety and efficacy of DOACs in this population is not known and their use should be avoided. The one exception is edoxaban, which can be dose reduced in patients < 60 kg (Table 1).

Heparin-Induced Thrombocytopenia

For patients with a recent or remote episode of heparin-induced thrombocytopenia (HIT), heparin therapy should be avoided. Although the only FDA-approved treatment for HIT is argatroban, in this setting, the clinician should consider using fondaparinux, a direct thrombin inhibitor, or possibly a DOAC, as a few cases series have demonstrated safety with the latter.[23] However, available data with DOACs and HIT are scant—there are ongoing trials in this patient population.

CONCLUSION

VTE is a common disorder and is associated with significant morbidity and mortality. DOACs have emerged as the treatment of choice for many patients given their convenience, predictable pharmacokinetics and pharmacodynamics, and their similar effectiveness in reducing VTE compared to VKAs, with significantly less major bleeding. There are some populations in which DOACs are not recommended or their safety and efficacy is not known. There are ongoing trials in many of these patient groups. When choosing the most appropriate treatment for patients, it is important for clinicians to understand the differences between the DOACs because they all have different dosing regimens. ■

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Disclosures: Receives institutional research grants from BMS; advisory board member for Janssen Pharmaceuticals and Dova; member of the PERT Consortium™ Board of Directors.

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