REVIEW ARTICLE

Optimizing the safety of treatment for venous thromboembolism in the era of direct oral anticoagulants

Jeffrey I. Weitz[1,2], Iqbal H. Jaffer[3]

1 Department of Medicine, McMaster University, Hamilton, Canada; Thrombosis and Atherosclerosis Research Institute, Hamilton, Canada
2 Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Canada
3 Department of Surgery, McMaster University, Hamilton, Canada; Thrombosis and Atherosclerosis Research Institute, Hamilton, Canada

KEY WORDS

bleeding risk, direct oral anticoagulants, periprocedural management, venous thromboembolism

ABSTRACT

Direct oral anticoagulants (DOACs) are rapidly replacing vitamin K antagonists (VKAs) for treatment of venous thromboembolism (VTE). The DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. When compared with conventional VTE treatment consisting of a parenteral anticoagulant followed by a VKA, the DOACs were equally effective for prevention of recurrence, but were associated with less bleeding. With similar efficacy, better safety, and the convenience of fixed dosing without the need for routine coagulation monitoring, guidelines now recommend DOACs over VKAs for VTE treatment in patients without active cancer. Nonetheless, measures are needed to optimize the safety of DOACs. Focusing on these measures, this paper summarizes the results of phase III trials evaluating DOACs for VTE treatment; identifies which VTE patients are or are not candidates for DOACs; provides guidance on how to choose among DOACs; lists the licensed dosing information for DOACs; discusses the optimal treatment duration for VTE; describes periprocedural management of DOACs in patients requiring surgery or intervention; and finally, reviews the management of bleeding, including the role for specific reversal agents.

Correspondence to:
Jeffrey I. Weitz, MD, Thrombosis and Atherosclerosis Research Institute, 237 Barton Street East, Hamilton, ON, L8L 2X2, Canada, phone: +1 905 574 8550, e-mail: weitzj@taari.ca
Received: September 4, 2016.
Accepted: September 4, 2016.
Published online: September 5, 2016.
Conflict of interests: JIW reports research support from Canadian Institutes of Health Research, Heart and Stroke Foundation, and Canadian Foundation for Innovation and consulting fees from Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Janssen Pharmaceuticals, Portola, IONIS Pharmaceuticals, and Merck. IHJ has research support from CCS-Bayer Vascular Resident Award and Boehringer Ingelheim.
Pol Arch Med Wewn. 2016; 126 (9): 688-696
doi:10.20452/pamw.3547

Introduction Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition that occurs for the first time in about 1 in 1000 persons each year and the incidence rises with age.[1,2] About one-third of patients with symptomatic VTE present with PE, while the remainder manifest as DVT.[3] Within 1 month of diagnosis, death occurs in approximately 6% of patients with DVT and 12% of those with PE.[4] Although VTE often occurs after surgery, with immobilization, or in patients with cancer, up to 50% of patients with VTE have no identifiable risk factors and are classified as having unprovoked VTE.[5] If anticoagulant therapy is stopped in patients with unprovoked VTE, the risk of recurrence is about 10% at 1 year and 30% at 5 years.[6] Recurrent DVT in the ipsilateral leg increases the risk of postthrombotic syndrome, a chronic disorder characterized by leg swelling and discomfort that occurs in 20% to 50% of DVT patients and can lead to venous ulcers in severe cases.[7] Chronic thromboembolic pulmonary hypertension occurs in 2% to 4% of patients with PE and can be fatal.[8] Therefore, VTE is a common disorder associated with significant morbidity and mortality.

Anticoagulants are the cornerstone of VTE treatment. The goal of therapy is to prevent thrombus extension or embolization, and to prevent new thrombi from forming. Conventional treatment starts with a rapidly acting parenteral anticoagulant, usually low-molecular-weight heparin (LMWH), which is overlapped with a vitamin K antagonist (VKA), such as warfarin. The parenteral anticoagulant is given for at least 5 days and is stopped when a therapeutic response to warfarin has been achieved as evidenced by an international normalized ratio (INR) between 2 and 3. Warfarin is then continued as long-term therapy for a minimum of 3 months. At this point, the decision to stop or continue treatment depends on the balance between the risk of recurrence if

warfarin is stopped and the risk of bleeding if it is continued. Patients with VTE in the setting of transient and reversible risk factors, such as surgery, have a low risk of recurrence if anticoagulant therapy is stopped at 3 months provided that they are fully mobile.[5] In contrast, those with ongoing risk factors, such as active cancer, and patients with unprovoked VTE are often prescribed extended anticoagulation therapy provided that the bleeding risk is not excessive. Therefore, anticoagulant treatment of VTE has been divided into 3 stages: initial therapy, long-term treatment, and extended anticoagulation.

Although conventional therapy is effective and safe, it is cumbersome because LMWH must be administered by subcutaneous injection, which is difficult for some patients, and warfarin requires frequent coagulation monitoring and dose adjustments to ensure that the INR is therapeutic. Such monitoring is cumbersome for patients and physicians and costly for health care systems. The limitations of warfarin prompted the development of direct oral anticoagulants (DOACs), which can be given in fixed doses and produce such a predictable anticoagulant response that routine coagulation monitoring is unnecessary. Because of their rapid onset of action, the DOACs enable all-oral regimens, which can replace parenteral anticoagulants and warfarin for initial, long-term, and extended VTE treatment.

Four DOACs are licensed for VTE treatment; these include dabigatran, which is an oral thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors. Their approvals were based on data from phase III trials demonstrating that the DOACs were as effective as conventional therapy for prevention of recurrence, but were associated with less bleeding. With similar efficacy, better safety, and the convenience of fixed dosing without the need for routine coagulation monitoring, guidelines now recommend the DOACs over VKAs for VTE treatment in patients without active cancer. Nonetheless, measures are needed to optimize the safety of the DOACs. Focusing on these measures, this paper summarizes the results of phase III trials evaluating DOACs for VTE treatment; identifies which VTE patients are or are not candidates for DOACs; provides guidance on how to choose among DOACs; lists the licensed dosing information for DOACs; discusses the optimal treatment duration for VTE; describes periprocedural management of DOACs in patients requiring surgery or intervention; and finally, reviews the management of bleeding, including the role for specific reversal agents.

Clinical trials of direct oral anticoagulants for venous thromboembolism treatment DOACs were compared with conventional anticoagulation therapy in 27 023 patients with acute VTE in 6 phase III randomized trials; RECOVER I and II with dabigatran,[9,10] EINSTEIN DVT and PE with rivaroxaban,[11,12] AMPLIFY with apixaban,[13] and HOKUSAI VTE with edoxaban.[14] The primary efficacy endpoint in these trials was recurrent VTE or VTE-related death, while the primary safety outcome was either major bleeding or the composite of major and clinically relevant nonmajor bleeding. In a pooled analysis of the 6 trials, recurrent VTE and VTE-related deaths occurred in 2.0% of DOAC recipients compared with 2.2% of those given a VKA (relative risk [RR], 0.90, 95% confidence interval [CI], 0.77–1.06).[15] Compared with VKAs, DOACs were associated with a 39% reduction in the risk of major bleeding (RR, 0.61; 95% CI, 0.45–0.83), a 63% reduction in intracranial bleeding (RR, 0.37; 95% CI, 0.21–0.68), and a 64% reduction in fatal bleeding (RR, 0.36; 95% CI, 0.15–0.84). In addition, clinically relevant nonmajor bleeding was reduced by 27% with the DOACs compared with VKAs (RR, 0.73; 95% CI, 0.58–0.93). Therefore, for acute VTE treatment, the DOACs are noninferior to well-managed VKA therapy, but are associated with significantly less bleeding.[15]

The design of the phase III trials with dabigatran and edoxaban differed from those with rivaroxaban and apixaban. Whereas dabigatran and edoxaban were started after a minimum of a 5-day course of parenteral anticoagulant therapy, rivaroxaban and apixaban were administered in all-oral regimens starting with a higher dose for 21 days and 7 days, respectively. When used in this all-oral fashion, both agents were noninferior to conventional therapy and were associated with significantly less major bleeding. Therefore, DOACs simplify VTE treatment and facilitate out-of-hospital management of most patients with DVT and many with PE, thereby reducing health care costs.

Rivaroxaban, apixaban, and dabigatran have been compared with placebo for secondary VTE prevention in patients who received at least 6 months of anticoagulant therapy for their index event in the EINSTEIN-extension,[11] AMPLIFY-EXT, and RE-SONATE trials,[16,17] respectively, and dabigatran was compared with warfarin for extended therapy in the RE-MEDY trial.[17] Pooled analyses of the 3 placebo-controlled trials revealed a significant reduction in the rate of recurrent VTE and VTE-related mortality with the DOACs compared with placebo, but an increased rate of major and clinically relevant nonmajor bleeding.[18,19] Unlike the other 2 trials, the AMPLIFY-EXT trial compared 2 dosing regimens of apixaban (2.5 mg and 5 mg twice daily) with placebo to identify the dose providing the best balance of efficacy and safety.[16] The risk of recurrent VTE with the lower-dose apixaban regimen was similar to that with the higher-dose regimen (RR, 0.97; 95% CI, 0.46–2.02), and neither regimen was associated with a significant increase in major bleeding compared with placebo, but there was a trend for less clinically relevant bleeding with the lower-dose regimen than with the higher-dose regimen (RR, 0.74; 95% CI, 0.46–1.22). These findings suggest a superior benefit-to-risk profile with the lower-dose apixaban regimen than with the high-dose

regimen. This is not the case with warfarin. Thus, in the ELATE trial, the rate of recurrent VTE was higher with lower-intensity warfarin (target INR of 1.5 to 2) than with usual-intensity warfarin (target INR of 2 to 3), while the rates of major bleeding were similar.[20] Because the risk of bleeding is often the limiting factor in the decision to extend the duration of anticoagulant therapy, the results with low-dose apixaban may prompt more clinicians to prescribe extended VTE treatment. The ongoing EINSTEIN CHOICE trial[21] is comparing 2 dosing regimens of rivaroxaban (10 mg and 20 mg once daily) with aspirin to identify the optimal dose of rivaroxaban for extended VTE treatment and to determine whether rivaroxaban is superior to aspirin for this purpose.

In the RE-MEDY study, dabigatran was noninferior to warfarin for extended VTE treatment (hazard ratio [HR], 1.44; 95% CI, 0.78–2.64), but was associated with a 46% reduction in the composite of major or clinically relevant nonmajor bleeding (HR, 0.54; 95% CI, 0.41–0.71).[17] Therefore, the DOACs are an effective, safe, and convenient option for initial, long-term, and extended VTE treatment.

Maximizing the benefits of direct oral anticoagulants in clinical practice Optimizing the efficacy and safety of DOACs depends on choosing the right drug for the right patient at the right dose and for the right duration. Proper periprocedural management of DOACs is also important to reduce the risk of bleeding.

Choosing the right anticoagulant for the right patient with venous thromboembolism When faced with a patient with acute VTE, the first question to ask is whether the patient is suitable for treatment with a DOAC. Patients requiring thrombolytic therapy for massive PE or extensive DVT are usually treated with unfractionated heparin to start, but can be switched to a DOAC when their condition stabilizes. DOACs should be avoided in patients with planned thrombolysis, antiphospholipid syndrome with a history of arterial thrombosis, in those with renal impairment (creatinine clearance <15 ml/min for rivaroxaban, apixaban and edoxaban and <30 ml/min for dabigatran), in those with severe hepatic impairment associated with coagulopathy, in patients who are younger than 18 years old, or in women who are pregnant or breast feeding.

VKAs remain the treatment of choice for VTE patients with a creatinine clearance of less than 15 ml/min and for those with antiphospholipid syndrome, particularly when it is associated with arterial thrombosis. Although the data with DOACs in patients with cancer-associated VTE are promising,[15] few such patients were included in randomized trials. Consequently, guidelines continue to recommend LMWH as the first-line therapy in patients with cancer-associated thrombosis.[22,23] However, ongoing trials are comparing DOACs with LMWH in such patients.

DOACs should probably not be used in patients with a body weight over 120 kg because data on their efficacy in such patients are lacking.[24] Patients who cannot afford the DOACs should receive conventional anticoagulant treatment because VKAs cost less than DOACs. Finally, if compliance is a concern, or if the patient is taking multiple medications that may interact with the DOACs, a VKA such as warfarin may be a better choice because INR monitoring will ensure therapeutic dosing.

Patients already on a VKA for VTE treatment should be switched to a DOAC if their INR is erratic. Switching can also be considered for patients who find INR testing and VKA dose adjustment burdensome, such as those with limited mobility or with active lifestyles. For extended treatment, the risk of bleeding is likely to be lower with DOACs than with VKAs, particularly if the dose intensity can be reduced, as was investigated with apixaban. Therefore, for patients who have already completed at least 6 months of anticoagulant treatment for their index VTE event, apixaban at a dose of 2.5 mg twice daily is a good choice. It remains to be established whether reduced dose regimens are effective for extended therapy with the other DOACs, and whether such regimens can be used in patients with a history of recurrent VTE.

Choosing a direct oral anticoagulant for venous thromboembolism treatment In VTE patients eligible for DOACs, there is no evidence to recommend one agent over another because head-to-head data are lacking. Nonetheless, guidance can be provided based on the distinct pharmacological profiles of the DOACs, the designs of the trials in which they were investigated, and patient characteristics (TABLE 1). Thus, for patients with a creatinine clearance between 15 and 50 ml/min, an oral factor Xa inhibitor may be a better choice than dabigatran because factor Xa inhibitors are less dependent on renal excretion. All-oral regimens streamline the transition of care from the clinic or the emergency department to home, and rivaroxaban and apixaban are the only agents that were evaluated in this manner. Selection between the two may depend on the ease of switching from the higher initial dose to the maintenance dose at 3 weeks and 1 week, respectively, and patient preference for a once- or twice-daily regimen thereafter. In contrast, dabigatran and edoxaban should only be prescribed after patients have received a minimum of a 5-day course of therapeutic doses of heparin or LMWH treatment. Rivaroxaban or apixaban may be good choices for patients over the age of 75 with reduced renal function (creatinine clearance of 30 to 50 ml/min), particularly females with low body weight, because the benefit-to-risk profile of these agents in such patients is superior to that of conventional therapy.[13,25] Dabigatran may not be the best choice in patients with a history of coronary artery disease because of its higher risk of myocardial infarction

TABLE 1 Choosing a direct oral anticoagulant

Characteristics	Drug choice	Rationale
CrCl, 15–50 ml/min	rivaroxaban, apixaban, or edoxaban	less affected by renal impairment than dabigatran
all-oral therapy	rivaroxaban or apixaban	dabigatran and edoxaban require heparin bridging
dyspepsia or upper GI complaints	rivaroxaban, apixaban, or edoxaban	dyspepsia with dabigatran in up to 10% of patients
recent GI bleed	apixaban	more GI bleeding with dabigatran, rivaroxaban, and high-dose edoxaban than with warfarin
significant CAD	rivaroxaban, apixaban, or edoxaban	small MI signal with dabigatran
poor compliance with twice-daily dosing	rivaroxaban or edoxaban	only agents given once daily

Abbreviations: CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastrointestinal; MI, myocardial infarction

TABLE 2 Licensed direct oral anticoagulant dosing regimens for treatment of venous thromboembolism

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
run-in period	LMWH for at least 5 days	15 mg BID for 21 days	10 mg BID for 7 days	LMWH for at least 5 days
subsequent dosing	150 mg BID	20 mg OD	5 mg BID	60 mg OD
renal adjustment	110 mg BID if ≥80 years old or moderate renal impairment	N/A	N/A	30 mg OD if CrCl 15–50 ml/min; weight <60 kg or potent P-gp inhibitors

Abbreviations: BID, twice daily; LMWH, low-molecular-weight heparin; OD, once daily; P-gp, P-glycoprotein; others, see TABLE 2

compared with warfarin.[26] Dabigatran should also be avoided in patients with upper gastrointestinal complaints because dyspepsia can occur in up to 10% of patients treated with this agent—a problem that tends to subside over time and can often resolve when the drug is taken with food. Except for apixaban and the 30-mg dose of edoxaban, the rate of gastrointestinal bleeding with the DOACs was higher than that with warfarin, particularly in the elderly.[27] Consequently, apixaban or low-dose edoxaban may be the best choice for patients with a recent history of gastrointestinal bleeding.

The risk of bleeding with DOACs is increased with concomitant use of antiplatelet agents, such as aspirin and nonsteroidal anti-inflammatory drugs, and these agents should be avoided if possible. For patients who must use aspirin, the daily dose of aspirin should not exceed 100 mg.

Choosing the right dose of direct oral anticoagulants To maximize efficacy, it is critical that the DOACs be used in the right dose (TABLE 2). Depending on the agent, regulators have provided clinicians with dosing recommendations defined by patient characteristics including advanced age, reduced renal function, low body weight, and concomitant administration of potent P-glycoprotein inhibitors—the factors associated with increased drug exposure and increased bleeding risk (TABLE 2). Despite clear dosing recommendations, however, observational data suggest that the lower doses of DOACs are overprescribed, potentially compromising their efficacy in clinical practice.[28] Education is needed to reverse this trend.

Optimal duration of venous thromboembolism treatment Optimizing the duration of anticoagulant therapy for VTE is important to minimize the risk of bleeding. All VTE patients require a minimum of 3 months of anticoagulant treatment. For patients with VTE provoked by a transient and reversible risk factor such as surgery, 3 months of anticoagulation is usually sufficient.[23] In contrast, patients with ongoing risk factors, such as active cancer, or those with unprovoked VTE are often given extended anticoagulation therapy because their risk of recurrence is high if treatment is stopped.[23] Therefore, many VTE patients require long-term anticoagulant therapy.

Periprocedural management in patients receiving direct oral anticoagulants Patients receiving long-term anticoagulant therapy often require elective surgery or invasive procedures, and appropriate perioperative management is important to minimize the bleeding hazard. To reduce the risk of bleeding complications, patients receiving a DOAC who require surgery associated with a moderate risk of bleeding should have the drug withheld for at least 24 hours. If the surgery is associated with a high risk of bleeding or if spinal anesthesia is planned, DOAC therapy should be stopped at least 48 hours before surgery.[29] Specific guidance is provided in the product labels regarding when to stop and restart DOACs before and after surgery,[30-33] as well as in practical guidelines.[29,34]

Assessment of the anticoagulant effect of the DOACs or quantification of plasma drug levels can help guide the timing of surgery (TABLE 3). These assessments depend on knowing which DOAC the patient was taking, and the results must be interpreted in relation to the timing of intake of the last dose of the DOAC and consideration of the impact of renal function on the half-life of the drug. Unfortunately, drug-specific tests are not widely or rapidly available in many hospitals.

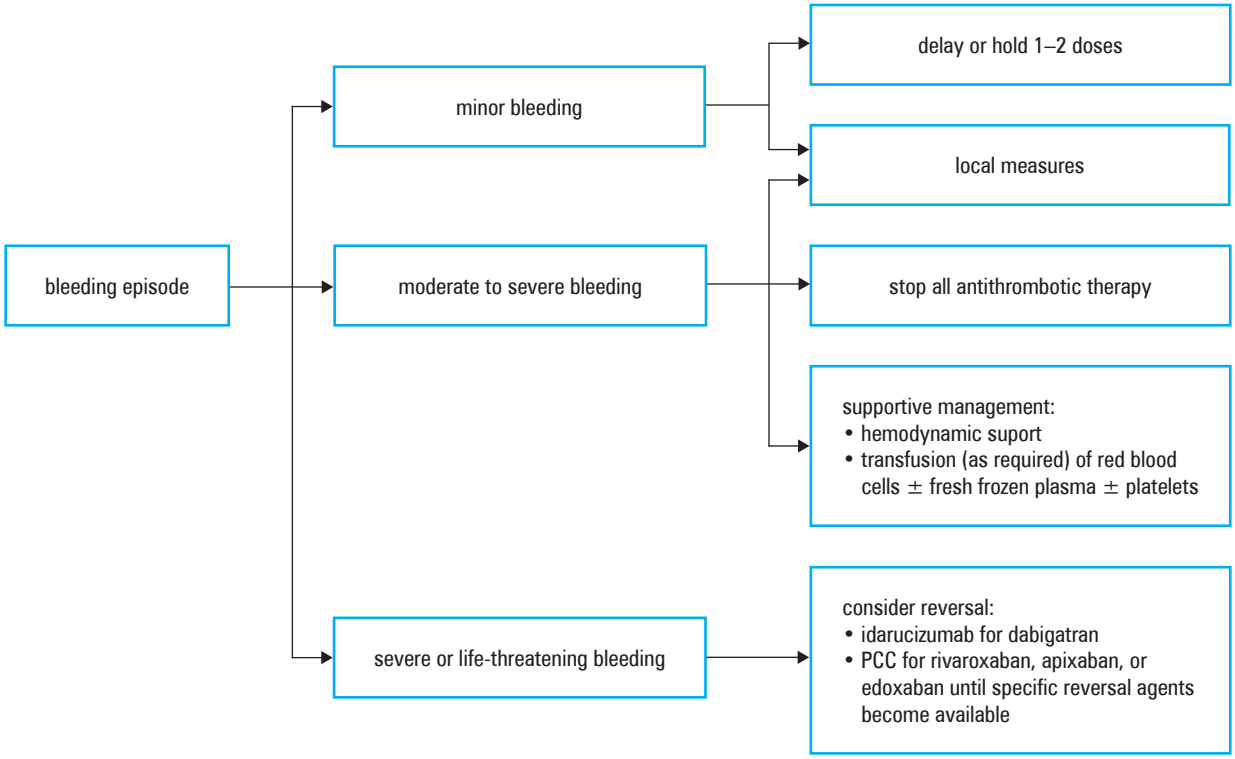

FIGURE 1 Management of bleeding in patients taking direct oral anticoagulants (DOACs). With minor bleeding, local measures and delaying or holding 1 to 2 doses is sufficient. With moderate to severe bleeding, the DOAC should be held, and supportive therapy should be administered. Reversal is indicated with severe or life-threatening bleeding; dabigatran can be reversed with idarucizumab and prothrombin complex concentrate (PCC) can be used for reversal of rivaroxaban, apixaban, and edoxaban until specific reversal agents, such as andexanet alfa and ciraparantag, are available.

Therefore, regulators and hospitals need to work together to address this gap.

Bleeding management in patients receiving direct oral anticoagulants Management of bleeding with DOACs is broadly similar to that with VKAs, but the mechanism of action and pharmacokinetic/pharmacodynamic profile of the specific drug must also be taken into account. When a bleeding event occurs, it is important to first assess its severity (ie, mild, moderate to severe, or severe and life-threatening) and location (critical or noncritical site). Mild bleeding (such as epistaxis) can usually be managed with local measures, but delaying the next dose or temporarily discontinuing treatment may be necessary for persistent bleeds.[35] Because of their short half-lives, discontinuation of DOAC therapy usually leads to rapid normalization of coagulation tests, provided that renal function is normal. The decision to temporarily or permanently discontinue anticoagulation should always be taken with a view to balance the risk of bleeding against the risk of thrombosis.

In patients with moderate to severe bleeding events, supportive therapy is the mainstay of management.[35] Because of the short half-life of the DOACs, most cases of bleeding will resolve within 12 hours provided that renal function is not severely compromised. The DOAC should be temporarily stopped as should concomitant long-acting antiplatelet agents (eg, clopidogrel, ticagrelor, or prasugrel) if possible. Renal function should be assessed by measuring the serum creatinine level and calculating the creatinine clearance. The anticoagulant effects or plasma levels of DOACs can be determined using commercially available and validated assays[36] to assess the contribution of the DOAC to the bleeding event.

Routine supportive measures should be applied. This includes hemodynamic support with fluid replacement and administration of blood products, such as packed red blood cells, fresh-frozen plasma and platelets if the patient has thrombocytopenia or if they were on long-acting antiplatelet agents (FIGURE 1). The location of bleeding should be identified. Gastrointestinal bleeding events, which occur into an open cavity, are rarely fatal and are less serious than bleeding into a closed space (eg, retroperitoneum or pericardium) or a critical organ (eg, intraocular bleed). Mechanical or surgical compression should be employed if possible and administration of tranexamic acid can be considered. In the event of a DOAC overdose, gastric lavage and activated charcoal can be used within 2 to 4 hours of ingestion.

An important aspect of bleeding management is to determine when reversal of the DOAC is indicated.[37] In addition to patients who are bleeding with the DOACs, reversal may be indicated in those requiring urgent surgery or intervention.

Indications for reversal of direct oral anticoagulant agents Reversal of DOACs should be considered in cases of life-threatening bleeding, such as intracranial hemorrhage (TABLE 4). Reversal should

TABLE 3 Assays to determine anticoagulant activity of direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
PT	✗	✓	✗	✗
aPTT	✓	✗	✗	✗
dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
anti-FXa assays	✗	✓	✓	✓

Abbreviations: aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, factor Xa; PT, prothrombin time

TABLE 4 Indications for reversal of direct oral anticoagulants

- need for urgent surgery or intervention that cannot be delayed for at least 8 hours
- life-threatening bleeding (eg, intracranial bleed)
- bleed into a critical organ (eg, intraocular bleed) or closed space (eg, pericardial or retroperitoneal bleed)
- ongoing bleeding
- expected long delay in restoration of hemostasis (eg, overanticoagulation with dabigatran in the setting of acute kidney injury)

be also considered when there is bleeding into a critical organ (eg, intraocular bleeding) or a closed space (eg, pericardial or retroperitoneal bleeding), when there is ongoing bleeding despite supportive measures and, particularly with dabigatran-associated bleeding, if there is serious bleeding in the setting of acute kidney injury where a long delay in drug clearance is expected. Reversal should also be considered in patients who require urgent surgery or interventions that are associated with a high risk of bleeding and that cannot be delayed for at least 8 to 12 hours to allow the DOACs to clear from the circulation.[37] Although reversal is best achieved with specific reversal agents, nonspecific prohemostatic agents, such as prothrombin complex concentrate (PCC) can be considered if specific agents are unavailable.[37]

Reversal agents for direct oral anticoagulant agents

Specific reversal agents include idarucizumab, which is specific for dabigatran, andexanet alfa, which reverses rivaroxaban, apixaban, edoxaban, and heparin, as well as ciraparantag, which reverses all of the DOACs and heparin (TABLE 5). Of these, idarucizumab is licensed and widely available in many hospitals, andexanet is under regulatory consideration, and ciraparantag has not yet been evaluated in patients. Until specific reversal agents for oral factor Xa inhibitors are available, PCC can be considered for their reversal.

Idarucizumab A Fab fragment of a humanized antibody against dabigatran, idarucizumab (Praxbind), binds dabigatran with a 350-fold higher affinity than thrombin to form a 1:1 stoichiometric complex that is cleared by the kidneys.[38] In healthy volunteers with normal or moderately impaired renal function, idarucizumab rapidly and completely reversed the anticoagulant effects of dabigatran.[38] Re-administration of dabigatran 24 hours after idarucizumab administration produced full anticoagulation, and idarucizumab has been given more than once to some volunteers without any loss of its activity. The ongoing RE-VERSE AD study[39] is enrolling dabigatran-treated patients with life-threatening or uncontrolled bleeding (Group A) or patients requiring emergency surgery or urgent procedures that cannot be delayed for at least 8 hours (Group B). All patients receive 5 grams of intravenous idarucizumab given as 2 boluses each of 2.5 grams no more than 15 minutes apart. Results in the first 90 patients (51 in Group A and 39 in Group B) were reported.[39] Idarucizumab rapidly reversed the anticoagulant effects of dabigatran in the 81 patients with abnormal coagulation tests at baseline. In the 35 patients in Group A where the time to cessation of bleeding could be assessed, hemostasis was restored at a mean of 11.4 hours. Of the 36 Group-B patients who underwent an intervention, 92% had normal hemostasis at the time of the procedure. One thrombotic event occurred within 72 hours of idarucizumab administration and 4 occurred later; anticoagulants had not been reinitiated in any of these patients.[39]

Andexanet alfa Andexanet alfa (AndexXa®) is a recombinant variant of human factor Xa that has its active site serine residue replaced with an arginine residue to eliminate catalytic activity and its membrane binding γ-carboxyglutamic acid domain removed to prevent incorporation in the prothrombinase complex.[40] Andexanet acts as a competitive inhibitor by binding rivaroxaban, apixaban, and edoxaban with affinities similar to that of native factor Xa, thereby serving as a decoy that sequesters the drugs until they can be cleared.[40] Andexanet also reverses the anticoagulant effects of heparin, LMWH, and fondaparinux by competing with factor Xa and thrombin for binding by the heparin-antithrombin complex.[41]

Because it also binds tissue factor pathway inhibitor (TFPI) to form a nonproductive complex, andexanet administration is associated with a reduction in TFPI activity and transient increases in the levels of prothrombin fragment 1.2, thrombin-antithrombin complexes, and D-dimer.[41] These changes are attenuated in subjects receiving oral factor Xa inhibitors because these agents compete with TFPI for andexanet binding. The clinical significance of these changes is uncertain; no thrombotic complications with andexanet have been reported to date.

In volunteers aged from 50 to 75 years, an intravenous andexanet bolus of 400 or 800 mg rapidly, but only transiently, reversed over 90% of the anti-factor Xa activity of apixaban and rivaroxaban.[42] More sustained reversal was achieved when the bolus was followed by a 2-hour intravenous infusion of andexanet at a dose of 4 and 8 mg/min, respectively.[42] Higher doses of andexanet are needed to reverse rivaroxaban than apixaban because the once-daily dosing of rivaroxaban results in higher drug concentrations and

TABLE 5 Features of specific reversal agents for direct oral anticoagulants

	Idarucizumab	Andexanet α	Ciraparantag
structure	recombinant humanized Fab fragment	recombinant human factor Xa variant	synthetic small molecule
molecular mass, Da	48000	39000	513
synthesis	expressed in Chinese hamster ovary cells	expressed in Chinese hamster ovary cells	chemical synthesis
mechanism of action	binds dabigatran with high affinity	competes with factor Xa for binding rivaroxaban, apixaban or edoxaban	binds DOACs via hydrogen bond formation
target	dabigatran	rivaroxaban, apixaban, and edoxaban	dabigatran, rivaroxaban, apixaban, and edoxaban
administration	intravenous bolus	intravenous bolus followed by 2-hour infusion	intravenous bolus
cost	$3500 per dose in the United States	unknown; likely to cost more than idarucizumab	unknown; likely to cost less than idarucizumab and andexanet

because the volume of distribution of rivaroxaban is greater than that of apixaban.

The ongoing ANNEXA-4 study is evaluating the efficacy and safety of andexanet reversal in patients taking rivaroxaban, apixaban, edoxaban, or enoxaparin who present with major bleeding.[43] More recently, the study has been extended to include patients requiring urgent surgery. The initial results in the first 67 patients were reported.[43] The mean age was 77 years and most presented with intracranial or gastrointestinal bleeding. Of these, 32 were taking rivaroxaban, 31 were taking apixaban and the remaining 4 were taking enoxaparin. In patients with baseline plasma rivaroxaban or apixaban concentrations over 75 ng/ml, andexanet decreased anti-factor Xa activity by 89% and 93% in those taking rivaroxaban and apixaban, respectively, after the bolus and during the infusion.[43] Four hours after the infusion stopped, there was a relative decrease of 39% and 30%, respectively, indicating a rebound increase in anti-factor Xa activity. Clinical hemostasis was good to excellent in 37 of the 47 patients in the efficacy analysis. Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up. Therefore, although promising, additional safety information regarding thrombotic events is needed as is information on the use of andexanet in patients requiring urgent surgery.[43]

Ciraparantag Ciraparantag (PER977) is a synthetic, water-soluble, cationic small molecule that was initially designed to bind to unfractionated heparin and LMWH via noncovalent hydrogen bonding and charge–charge interactions.[44] Later, dynamic light scattering studies revealed that the drug also binds dabigatran, rivaroxaban, apixaban, and edoxaban.[44] In rats given dabigatran, edoxaban, or enoxaparin, ciraparantag attenuated tail bleeding in this animal model and normalized the time to clot formation, as measured by thromboelastography.[44]

In healthy volunteers given one-time doses of edoxaban (60 mg) or enoxaparin (1.5 mg/kg), a single bolus of ciraparantag shortened the prolonged whole blood clotting time in a concentration-dependent manner.[45,46] The effect persisted for 24 hours, and there was no increase in the levels of D-dimer or thrombin–antithrombin complexes suggestive of a procoagulant state. The whole blood clotting time was used to monitor the effect of ciraparantag in these studies because ciraparantag binds citrate, the reagent into which blood is collected for coagulation testing. This phenomenon precludes measurement of routine tests of coagulation or anti-factor Xa activity in subjects given ciraparantag.[45,46] Unfortunately, the whole blood clotting time is not available in most hospitals. To overcome this problem, a point-of-care microfluidic device has been developed to measure the whole blood clotting time. However, this device has not yet received regulatory approval. Phase III studies with ciraparantag have not been initiated so the development of this agent lags behind that of andexanet alfa.

Prothrombin complex concentrate Several studies have shown that 3- or 4-factor PCC at least partially reverses the prothrombin time and enhances thrombin generation in volunteers given rivaroxaban or apixaban.[47] Furthermore, in volunteers given edoxaban, 4-factor PCC attenuated bleeding from punch biopsy sites in a concentration-dependent manner.[48] With 50 U/kg, PCC restored bleeding duration to background levels and enhanced thrombin generation. Although these findings are promising, the efficacy of PCC in patients taking oral factor Xa inhibitors who present with serious bleeding is unknown. Nonetheless, until specific reversal agents for rivaroxaban, apixaban, and edoxaban are available, PCC is a reasonable choice for such patients.

Conclusions and future directions

DOACs are at least as effective as VKAs, while being safer and more convenient. As such, they are revolutionizing our approach to VTE treatment. Postmarketing studies suggest that the favorable results of clinical trials can readily be translated into practice. Nonetheless, to optimize safety there remains a need for selection of the appropriate patient, drug, and dose, as well as a careful follow-up.

The fear of uncontrolled bleeding has been lifted with the introduction of idarucizumab for dabigatran reversal. Licensing of reversal agents for oral factor Xa inhibitors will provide additional reassurance.

Although DOACs represent a major advance in VTE treatment, gaps persist. For example, more information is needed about their utility in VTE patients with active cancer, their efficacy and safety in patients with a creatinine clearance between 15 and 30 ml/min, and optimal dosing in obese and pediatric patients. Such information is important because the DOACs are now being evaluated for multiple new indications. Therefore, as the use of DOACs continues to increase, ongoing efforts are needed to maximize safety.

Acknowledgments Dr. Weitz holds the Canada Research Chair (Tier I) in Thrombosis and the Heart and Stroke Foundation J. Fraser Mustard Chair in Cardiovascular Research at McMaster University, Hamilton, Ontario, Canada.

REFERENCES

1 Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolysis. 2009; 28: 401-409.

2 White RH. The epidemiology of venous thromboembolism. Circulation. 2003; 107: SI4-SI8.

3 Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998; 158: 585-593.

4 Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med. 1999; 159: 445-453.

5 Kearon C. Natural history of venous thromboembolism. Circulation. 2003; 107: SI22-SI30.

6 Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1 626 patients. Haematologica. 2007; 92: 199-205.

7 Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996; 125: 1-7.

8 Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004; 350: 2257-2264.

9 Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361: 2342-2352.

10 Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2013; 129: 764-772.

11 Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363: 2499-2510.

12 Buller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012; 366: 1287-1297.

13 Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369: 799-808.

14 Buller HR, Decousus H, Grosso M, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369: 1406-1415.

15 van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014; 124: 1968-1975.

16 Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368: 699-708.

17 Schulman S, Kearon C, Kakkar AK, et al. Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. N Engl J Med. 2013; 368: 709-718.

18 Sindet-Pedersen C, Pallisgaard JL, Olesen JB, et al. Safety and efficacy of direct oral anticoagulants compared to warfarin for extended treatment of venous thromboembolism-a systematic review and meta-analysis. Thromb Res. 2015; 136: 732-738.

19 Marik PE, Cavallazzi R. Extended anticoagulant and aspirin treatment for the secondary prevention of thromboembolic disease: A systematic review and meta-analysis. PLoS One. 2015; 10: e0143252.

20 Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003; 349: 631-639.

21 Weitz JI, Bauersachs R, Beyer-Westendorf J, et al. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism. Rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost. 2015;114: 645-650.

22 Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. J Clin Oncol. 2015; 33: 654-656.

23 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016; 149: 315-352.

24 Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2016; 14: 1308-1313.

25 Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013; 11: 21.

26 Eikelboom JW, Weitz JI. Anticoagulation therapy. Dabigatran and risk of myocardial infarction. Nat Rev Cardiol. 2012; 9: 260-262.

27 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383: 955-962.

28 Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation. 2015; 131: 157-164.

29 Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. N Engl J Med. 2013; 368: 2113-2124.

30 Boehringer-Ingelheim. Product Monograph: Pradaxa 2016. Available from: http://www.boehringeringelheim.ca/content/dam/internet/opu/ca_EN/documents/humanhealth/product_monograph/PradaxaPMEN.pdf. Accessed August 31, 2016.

31 Bayer. Product Monograph: Xarelto 2016. Available from: http://www.bayer.ca/omr/online/xarelto-pm-en.pdf. Accessed August 31, 2016.

32 Pfizer. Product Monograph: Eliquis 2016. Available from: http://www.pfizer.ca/sites/g/files/g10028126/f/201607/ELIQUIS_PM_184464_16June2016_E_marketed.pdf. Accessed August 31, 2016.

33 Daiichi-Sankyo. Prescribing Information: Savaysa 2016. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed August 31, 2016.

34 Benzon HT, Avram MJ, Green D, et al. New oral anticoagulants and regional anaesthesia. Br J Anaesth. 2013; 111: SI96-SI113.

35 Weitz JI, Pollack CV Jr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. Thromb Haemost. 2015; 114: 1113-1126.

36 Pollack CV Jr. Coagulation assessment with the new generation of oral anticoagulants. Emerg Med J. 2016; 33: 423-340.

37 Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016; 14: 623-627.

38 Eikelboom JW, Quinlan DJ, van Ryn J, et al. Idarucizumab: the antidote for reversal of dabigatran. Circulation. 2015; 132: 2412-2422.

39 Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015; 373: 511-520.

40 Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013; 19: 446-351.

41 Yeh CH, Fredenburgh JC, Weitz JI. The real decoy: an antidote for factor Xa-directed anticoagulants. Circ Res. 2013; 113: 954-957.

42 Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015; 373: 2413-2424.

43 Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016. [Epub ahead of print].

44 Sullivan DW Jr, Gad SC, Laulicht B, et al. Nonclinical safety assessment of PER977: a small molecule reversal agent for new oral anticoagulants and heparins. Int J Toxicol. 2015; 34: 308-317.

45 Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med. 2014; 371: 2141-2142.

46 Ansell JE, Laulicht BE, Bakhru SH, et al. Ciraparantag safely and completely reverses the anticoagulant effects of low molecular weight heparin. Thromb Res. 2016.

47 Baumann Kreuziger LM, Keenan JC, Morton CT, et al. Management of the bleeding patient receiving new oral anticoagulants: a role for prothrombin complex concentrates. Biomed Res Int. 2014; 2014: 583794.

48 Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation. 2015; 131: 82-90.

ARTYKUŁ POGLĄDOWY

Optymalizacja bezpieczeństwa leczenia żylnej choroby zakrzepowo-zatorowej w dobie doustnych antykoagulantów niebędących antagonistami witaminy K

Jeffrey I. Weitz[1,2], Iqbal H. Jaffer[3]

1 Department of Medicine, McMaster University, Hamilton, Canada; Thrombosis and Atherosclerosis Research Institute, Hamilton, Kanada
2 Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Kanada
3 Department of Surgery, McMaster University, Hamilton, Canada; Thrombosis and Atherosclerosis Research Institute, Hamilton, Kanada

SŁOWA KLUCZOWE

ryzyko krwawienia, doustne antykoagulanty niebędące antagonistami witaminy K (NOAC), terapia okołozabiegowa, żylna choroba zakrzepowo-zatorowa (ŻChZZ)

Adres do korespondencji: Jeffrey I. Weitz, MD, Thrombosis and Atherosclerosis Research Institute, 237 Barton Street East, Hamilton, ON, L8L 2X2, Canada, phone: +1905 574 8550, e-mail: weitzj@taari.ca

Praca wpłynęła: 04.09.2016.
Przyjęta do druku: 04.09.2016.
Publikacja *online*: 05.09.2016.
Zgłoszono sprzeczność interesów: JIW otrzymuje wsparcie na badania od Canadian Institutes of Health Research, Heart and Stroke Foundation oraz Canadian Foundation for Innovation, a także wynagrodzenie za konsultacje od firm Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Janssen Pharmaceuticals, Portola, IONIS Pharmaceuticals oraz Merck. IHJ otrzymuje wsparcie na badania od CCS-Bayer Vascular Resident Award oraz Boehringer Ingelheim.
Pol Arch Med Wewn. 2016; 126 (9): 688-696
doi:10.20452/pamw.3547
Tłumaczył dr Tomasz Imiela

STRESZCZENIE

Antykoagulanty niebędące antagonistami witaminy K (*non-vitamin K oral anticoagulants* – NOAC) coraz częściej zastępują antagonistów witaminy K (*vitamin K antagonists* – VKA) w leczeniu żylnej choroby zakrzepowo-zatorowej (ŻChZZ). Do NOAC zalicza się dabigatran (inhibitor trombiny) oraz rywaroksaban, apiksaban i edoksaban, które hamują aktywność czynnika Xa. W porównaniu z konwencjonalną metodą leczenia ŻChZZ najpierw antykoagulantem podawanym pozajelitowo, a potem VKA, terapia NOAC równie skutecznie zapobiega nawrotom tej choroby i wiąże się z mniejszym ryzykiem krwawienia. Ponadto zapewnia podobną efektywność, jest bezpieczniejsza i pozwala na dogodne ustalenie dawkowania bez potrzeby rutynowego monitorowania procesu koagulacji. Według wytycznych, w leczeniu pacjentów z ŻChZZ bez aktywnego procesu nowotworowego zaleca się stosowanie NOAC zamiast VKA. Niemniej jednak, potrzebne są narzędzia do optymalizacji bezpieczeństwa terapii w trakcie leczenia NOAC. Artykuł podsumowuje wyniki badań klinicznych fazy III określające skuteczność leczenia ŻChZZ za pomocą NOAC, wskazuje, którzy pacjenci z ŻChZZ nie powinni być poddani terapii NOAC, i udziela wskazówek w zakresie wyboru odpowiedniego NOAC. Praca zawiera również informacje na temat zalecanego dawkowania, a także optymalnego czasu leczenia ŻChZZ, opis okołozabiegowej terapii NOAC przeprowadzonej wśród pacjentów, którzy wymagają zabiegu operacyjnego lub interwencji chirurgicznej, i zarys postępowania w przypadku krwawienia z uwzględnieniem roli poszczególnych środków odwracających efekt terapii.