

Expanding use of new oral anticoagulants

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Abstract

New, non-vitamin K antagonist oral anticoagulants (NOACs) have been developed to overcome the limitations of warfarin. These include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. In the US, rivaroxaban and apixaban are licensed for thromboprophylaxis after elective hip or knee arthroplasty, and rivaroxaban and dabigatran are approved for treatment of venous thromboembolism. Dabigatran, rivaroxaban, and apixaban also are licensed for stroke prevention in eligible patients with atrial fibrillation. Designed to be given in fixed doses without routine coagulation monitoring, the NOACs are more convenient to administer than warfarin. Phase III clinical trials have shown that the NOACs are at least as effective as warfarin and are associated with less intracranial bleeding. This article compares the pharmacological properties of the NOACs with those of warfarin, describes the clinical trial data with the NOACs in the approved indications, outlines the unmet medical needs that the NOACs address, highlights the potential limitations of the NOACs, and provides guidance on the optimal use of the NOACs.

Introduction

Anticoagulants are widely used for the prevention and treatment of venous and arterial thrombosis. For chronic indications, oral anticoagulants are preferred over parenteral agents. Until recently, the vitamin K antagonists (VKAs), such as warfarin, were the only available oral anticoagulants. Though effective, warfarin has numerous limitations, which complicate its management. Thus, warfarin has a slow onset and offset of action, and the dose of warfarin varies, reflecting differences in dietary vitamin K intake, multiple drug-drug interactions, and common genetic polymorphisms that influence its pharmacokinetic or pharmacodynamic profile [1]. The variable anticoagulant effect of warfarin is problematic because it has a narrow therapeutic window; under-anticoagulation is associated with a risk of thrombosis, whereas over-anticoagulation increases the risk of bleeding. Consequently, frequent monitoring of the international normalized ratio (INR) is necessary to ensure that warfarin has achieved a therapeutic anticoagulant effect. Such monitoring is burdensome for patients and physicians and costly for the health-care system.

NOACs were developed to overcome the limitations of warfarin. These agents include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. NOACs have a rapid onset and offset of action and produce a more predictable anticoagulant response than warfarin because dietary vitamin K intake has no impact on the activity of the NOACs and because drug-drug interactions are infrequent. Consequently, NOACs can be administered in fixed doses without routine coagulation monitoring, thereby streamlining anticoagulant therapy. Because they are easier to administer, NOACs are replacing warfarin for many indications.

Currently, rivaroxaban and apixaban are licensed in the US for thromboprophylaxis after elective hip or knee arthroplasty; dabigatran and rivaroxaban are approved for the treatment of venous thromboembolism (VTE); and dabigatran, rivaroxaban, and apixaban are licensed for stroke prevention in patients with atrial fibrillation. In each of these indications, the NOACs fulfil an unmet medical need, and data from clinical trials have highlighted the

opportunities and challenges associated with their use. Focusing on the emerging role of the NOACs in the prevention and treatment of thrombosis, this review (a) compares the pharmacological properties of the NOACs with those of warfarin, (b) briefly describes the clinical trial data with the NOACs in the three approved indications, (c) highlights the advantages of the NOACs over conventional treatment in each indications, (d) outlines the challenges with the NOACs and identifies new areas of research aimed at addressing these challenges, and (e) provides perspective on the optimal use of the NOACs.

Comparison of the pharmacological properties of new oral anticoagulants with those of warfarin

As outlined in Table 1, warfarin acts as an anticoagulant by reducing the function of the vitamin K-dependent clotting proteins, factors II, VII, IX, and X, thereby attenuating the extrinsic, intrinsic, and common pathways of blood coagulation. In contrast, the NOACs inhibit only a single target—either factor Xa or thrombin (Figure 1)—and have a rapid onset of action such that peak plasma levels are achieved 1 to 4 hours after oral administration [2]. With half-lives of about 12 hours, the NOACs also have a rapid offset of action.

Whereas warfarin is cleared predominantly through non-renal mechanisms, the NOACs are excreted, at least in part, via the kidneys. The extent of renal clearance varies depending on the agent; about 80% of dabigatran is cleared unchanged by the kidneys, whereas 50%, 33%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared unchanged via the renal route. Because of their renal clearance, NOACs should be used with caution in patients with a creatinine clearance of less than 30 mL/min and should not be used in those with a creatinine clearance of below 15 mL/min. Although it is possible that the hepatic metabolism of apixaban and rivaroxaban compensate for renal excretion in patients

with end-stage renal disease, NOACs should be avoided until efficacy and safety data are available in such patients.

Drug-drug interactions are few with the NOACs, in contrast to VKAs, and there are no dietary restrictions, except that, when given in treatment doses, rivaroxaban should be administered with a meal to maximize its absorption. Vitamin K is the antidote for warfarin. When given orally, vitamin K will restore the INR to baseline levels, but this often takes more than 24 hours. Intravenous administration of vitamin K results in more rapid lowering of the INR, and an effect is seen within 6 hours. In patients with serious bleeding, four-factor prothrombin complex concentrate (PCC) should be given to restore the INR to baseline levels. PCC is preferred over fresh frozen plasma because PCC provides rapid and complete reversal of the anticoagulant effect of warfarin without concerns about volume overload or the potential allergic or infectious complications of plasma. There are no specific antidotes for the NOACs, but these are under development. Although PCC or recombinant factor VIIa may be effective for reversal of the NOACs, clinical data are lacking. In patients with serious bleeding who have developed renal failure, dialysis can be used to remove dabigatran. Because rivaroxaban and apixaban are highly protein-bound, dialysis will not remove them.

Clinical trial data with new oral anticoagulants

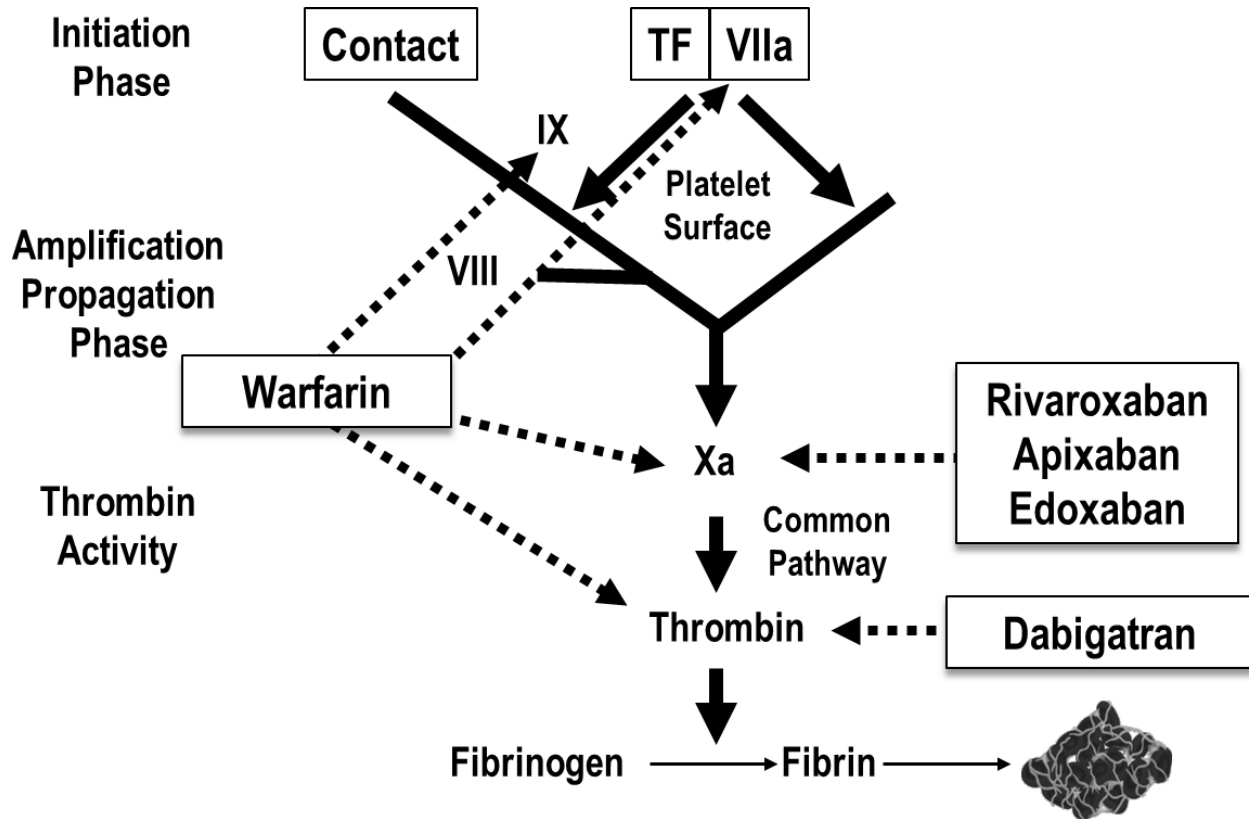
Clinical evaluation of the NOACs started in patients undergoing elective hip or knee arthroplasty and this was the first indication for which an NOAC was licensed. Subsequent phase II studies in atrial fibrillation or acute VTE treatment informed the doses selected for the phase III trials in these indications. The results of the phase III trials for each of the licensed indications are briefly discussed with an emphasis on the potential benefits of NOACs over conventional therapy.

Table 1. Comparison of the pharmacological properties of warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	VKORC1	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Bioavailability, percentage	100	7	80	60	62
Dosing	OD	BID	OD (BID)	BID	OD
Time to peak effect	4-5 days	1-3 hours	2-4 hours	1-2 hours	1-2 hours
Half-life, hours	40	14-17	7-11	8-14	5-11
Renal clearance as unchanged drug	None	80%	33%	27%	50%
Monitoring	Yes	No	No	No	No
Interactions	Multiple	P-gp	3A4/P-gp	3A4/P-gp	P-gp

3A4, cytochrome P₄₅₀ 3A4 isoenzyme; BID, twice daily; OD, once daily; P-gp, P-glycoprotein; VKORC1, C1 subunit of the vitamin K epoxide reductase enzyme.

Figure 1. Sites of action of warfarin and the new oral anticoagulants



TF, tissue factor.

Elective hip or knee arthroplasty

Elective hip or knee arthroplasty is an increasingly common orthopedic procedure. A nationwide inpatient survey identified a 37% increase in the number of patients undergoing hip arthroplasty from 2000 to 2004 and a 54% increase in the number undergoing knee arthroplasty [3]. It is estimated that, by 2015, elective hip and knee arthroplasty will be performed in 600,000 and 1.4 million patients, respectively [4].

Patients undergoing elective hip or knee arthroplasty are at risk for VTE, which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE). On average, the rate of symptomatic VTE 90 days after such surgery is about 3.6% and the rate of fatal PE is 0.13% [5–7]. A recent meta-analysis suggests that the rates of symptomatic VTE prior to discharge from the hospital in patients undergoing hip or knee arthroplasty are 0.5% and 1.1%, respectively [8]. However, results from a global registry indicate that the median length of stay for these patients has been reduced to 3 to 4 days, respectively [9]. In contrast, the mean times to symptomatic VTE after hip or knee arthroplasty are 9.7 and 21.5 days, respectively [10]. Therefore, VTE in these

patients is primarily an outpatient problem, thereby highlighting the need for prolonged thromboprophylaxis after surgery.

Current guidelines recommended post-operative thromboprophylaxis with low-molecular-weight heparin (LMWH), fondaparinux, or warfarin (dose-adjusted to an INR of 2 to 3) for at least 10 days after elective hip or knee arthroplasty and for up to 35 days [11]. The problem with these agents is that LMWH and fondaparinux require daily subcutaneous injection, which can be difficult for patients to manage after hospital discharge, whereas warfarin requires frequent monitoring and dose adjustment at a time when limited mobility complicates visits to the laboratory for INR testing. Consequently, adherence with extended thromboprophylaxis is often suboptimal.

Dabigatran, rivaroxaban, and apixaban have been compared with enoxaparin for post-operative thromboprophylaxis in patients undergoing elective hip or knee arthroplasty. The pooled data [12] show that rivaroxaban significantly reduces the rate of VTE compared with enoxaparin (pooled relative risk [RR] 0.56, 95% confidence

interval [CI] 0.43 to 0.73; $P < 0.0001$) but is associated with a potential for an increased risk of major bleeding (pooled RR 1.26, 95% CI 0.94 to 1.69; $P = 0.13$), whereas dabigatran provides no significant advantage over enoxaparin for reduction of VTE (pooled RR 1.10, 95% CI 0.90 to 1.35; $P = 0.34$) and is associated with similar rates of major bleeding. The results with apixaban are mixed; when compared with once-daily enoxaparin (40 mg once daily) in patients undergoing hip or knee arthroplasty, apixaban significantly reduced the risk of VTE by 0.8% (95% CI 1.2 to 0.3; $P < 0.001$) without increasing the risk of major bleeding [13]. In contrast, when compared with twice-daily enoxaparin (30 mg twice daily) in patients undergoing knee arthroplasty [14], apixaban was not more effective for VTE prevention (RR 1.02, 95% CI 0.78 to 1.32; $P = 0.06$).

Overall, the efficacy and safety of the NOACs and enoxaparin are similar. The major advantage of the NOACs is that they can be given orally in fixed doses once or twice daily, thereby streamlining out-of-hospital thromboprophylaxis by obviating the need for daily subcutaneous injections or coagulation monitoring. In addition, the NOACs are less expensive than enoxaparin. Therefore, NOACs represent a more convenient and potentially more cost-effective option than enoxaparin for extended thromboprophylaxis after elective hip or knee arthroplasty [15].

Venous thromboembolism treatment

Anticoagulants are the cornerstone of VTE treatment. Traditionally, treatment starts with a rapidly acting parenteral anticoagulant, usually LMWH, which is overlapped with warfarin for at least 5 days. The parenteral anticoagulant is stopped when the INR reaches 2 or higher, and then warfarin is continued long-term 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 [16]. 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 [17], whereas 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, conventional anticoagulant treatment of VTE has been divided into three stages: (a) initial therapy for 5 to 10 days, the goal of which is to prevent thrombus extension and fatal PE; (b) long-term therapy for 3 months, which is given to prevent recurrent VTE and to reduce the risk of complications, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension; and (c) extended therapy beyond 3 months, which is administered when the risk

of recurrent VTE is high and exceeds the risk of major bleeding with anticoagulant treatment.

Though effective, traditional treatment of VTE is cumbersome because initial therapy with LMWH requires daily subcutaneous injection, whereas warfarin requires frequent INR monitoring and dose adjustments. There is increasing evidence that the majority of patients with DVT and low-risk patients with PE can safely be treated at home [16]. Because of the complexity of initial anticoagulant therapy, however, many such patients are hospitalized, which increases health-care costs [18]. Therefore, by simplifying VTE treatment, NOACs facilitate transition of care from the emergency department or the hospital to home.

In patients with acute VTE, dabigatran, rivaroxaban, apixaban, and edoxaban were compared with conventional treatment in the RE-COVER I and II, EINSTEIN-DVT and -PE, AMPLIFY, and Hokusai-VTE trials, respectively [19–24]. The primary efficacy outcome of these trials was recurrent VTE, and the primary safety outcome was major bleeding or the composite of major or clinically relevant non-major bleeding.

The risk of recurrence is highest in the first month after VTE diagnosis [25]. Phase II VTE treatment studies with rivaroxaban and apixaban not only helped to identify the doses to be carried into phase III but also provided reassurance that an all-oral approach was possible. Consequently, the EINSTEIN-DVT and -PE trials and the AMPLIFY trial used oral regimens that started with more intensive therapy for 3 weeks and 7 days, respectively (Table 2). In contrast, phase II studies in VTE treatment were not conducted with dabigatran or edoxaban; instead, doses for the RE-COVER and Hokusai-VTE trials were selected on the basis of the results of phase II studies in atrial fibrillation. Without evidence supporting the immediate use of dabigatran or edoxaban in acute VTE, treatment regimens in the RE-COVER and Hokusai-VTE trials started with a parenteral anticoagulant, which was administered for at least 5 days, and then patients were transitioned to warfarin or given dabigatran or edoxaban, respectively. Treatment duration varied among the trials; it was fixed at 6 months in the RE-COVER and AMPLIFY trials and was flexible at 3, 6, or 12 months in the EINSTEIN-DVT, EINSTEIN-PE, and Hokusai-VTE trials.

In a recent meta-analysis of the five phase III trials comparing NOACs with warfarin [26], which included 24,455 patients with acute VTE, rates of recurrent VTE, fatal PE, and all-cause mortality were not significantly lower with the NOACs (RR 0.88, 95% CI 0.74 to 1.05; RR 1.02, 95% CI 0.39 to 5.96; and RR 0.97, 95% CI 0.83 to

Table 2. Recommended doses for new oral anticoagulants for the licensed indications

Drug	VTE prevention	VTE treatment	Atrial fibrillation
Rivaroxaban	10 mg once daily with or without food. Use with caution with creatinine clearance of less than 30 mL/min.	15 mg twice daily for 21 days followed by 20 mg once daily thereafter with food. Use with caution in those with a creatinine clearance of less than 30 mL/min.	20 mg once daily with food; 15 mg once daily with food for those with a creatinine clearance of 15 to 50 mL/min
Apixaban	2.5 mg twice daily	Not licensed	5 mg twice daily; 2.5 mg twice daily with at least two of the following, age 80 years or more; body weight 60 kg or less, and serum creatinine of 1.5 mg/dL or higher
Dabigatran	Not licensed	150 mg twice daily after a 5- to 10-day course of parenteral anticoagulation	150 mg twice daily; 75 mg twice daily in those with a creatinine clearance of 15 to 30 mL/min
Edoxaban	Not licensed	Not licensed	Not licensed

VTE, venous thromboembolism.

1.14, respectively). However, the rate of major bleeding was significantly lower with the NOACs than with warfarin (RR 0.60, 95% CI 0.41 to 0.88), as was the rate of fatal bleeding (RR 0.36, 95% CI 0.15 to 0.87). The numbers needed to treat with NOACs instead of warfarin to prevent one major bleed or one fatal bleed were 149 and 1,111, respectively [26]. A fixed-effect network analysis did not reveal significant differences between any one NOAC and rivaroxaban [26]. Overall, therefore, NOACs are non-inferior to conventional therapy for VTE treatment and are associated with less bleeding. Furthermore, NOACs are more convenient to administer. Rivaroxaban and apixaban can be given in all-oral regimens that obviate the need for a parenteral anticoagulant at the outset, and all of the NOACs are easier to administer than warfarin because they can be given in fixed doses without the need for routine coagulation monitoring.

For extended VTE treatment, rivaroxaban, apixaban, and dabigatran were compared with placebo in the EINSTEIN-EXTENSION, AMPLIFY-Extension, and RE-SONATE trials, respectively [21,27,28]. Patients enrolled in the EINSTEIN-EXTENSION and AMPLIFY-Extension studies had received 6 to 12 months of anticoagulation therapy for their index VTE event, whereas those in the RE-SONATE study had received 6 to 18 months of treatment. Whereas single-dose regimens of rivaroxaban and dabigatran were evaluated in the EINSTEIN-EXTENSION and RE-SONATE trials, two dosage regimens of apixaban were studied in the AMPLIFY-Extension trial. All of the trials were powered to demonstrate superiority of the NOACs over placebo, and the primary efficacy outcome was recurrent VTE or VTE-related mortality.

Dabigatran is the only agent to be compared with warfarin for extended VTE treatment in the RE-MEDY trial [28]. Patients enrolled in this trial had received 3 to 12 months of anticoagulant treatment for their index VTE event, and the study was designed to show non-inferiority of dabigatran compared with warfarin. Although edoxaban

has yet to be evaluated in an extension study, the drug has been administered for up to 12 months because of the flexible treatment duration in the Hokusai-VTE trial.

Dabigatran, rivaroxaban, and apixaban were superior to placebo for prevention of recurrent VTE and were associated with low rates of major bleeding. Compared with placebo, both the treatment and the prophylactic dose of apixaban (5 and 2.5 mg twice daily, respectively) significantly reduced the risk of recurrent VTE. Although both dose regimens were associated with low rates of major bleeding, there was a trend for less clinically relevant non-major bleeding with the lower-dose apixaban regimen. This finding raises the possibility that the intensity of treatment with NOACs can be lowered for extended VTE treatment to reduce the risk of bleeding without compromising efficacy. In contrast, attempts to lower the intensity of warfarin therapy for extended VTE treatment resulted in reduced efficacy without evidence of less bleeding.

Dabigatran was non-inferior to warfarin for extended VTE treatment in the RE-MEDY trial and was associated with less bleeding [28]. Although the number of events was small, myocardial infarction was more common with dabigatran than with warfarin, a phenomenon observed in other studies that compared dabigatran with warfarin. The clinical relevance of this finding is uncertain, however, because the rates of all-cause mortality and cardiovascular mortality tend to be lower with dabigatran than with warfarin. Overall, therefore, NOACs are effective and safe for initial, long-term, and extended VTE treatment.

Atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia. One in four persons over the age of 40 years will develop atrial fibrillation during their lifetime, and it is estimated that, by the year 2050, up to 16 million persons in the US will have atrial fibrillation [29]. Atrial

fibrillation is a major health-care problem because it is associated with a five-fold increase in the risk of ischemic stroke, and strokes in patients with atrial fibrillation are more likely to be fatal or disabling than those in patients without atrial fibrillation. For this reason, most patients with atrial fibrillation should receive anticoagulant therapy to reduce the risk of stroke.

Traditionally, warfarin has been used for stroke prevention in patients with atrial fibrillation. Compared with control, warfarin reduces the risk of stroke and systemic embolism by about 64% and reduces mortality by about 25% [30]. However, because of the complexity of warfarin management, it is estimated that at least half of eligible atrial fibrillation patients are not receiving anticoagulant therapy, and in those who are taking warfarin, the INR is frequently outside the therapeutic range [31,32]. Because of the increased risk of stroke, underuse of and poor adherence to warfarin therapy are costly to the health-care system [33]. The problems with warfarin prompted trials with the NOACs in patients with atrial fibrillation.

Dabigatran, rivaroxaban, apixaban, and edoxaban were compared with warfarin in 71,683 patients with atrial fibrillation in four phase III trials, which were powered to demonstrate non-inferiority of the NOACs. The primary efficacy endpoint in these trials was the composite of stroke (both ischemic and hemorrhagic) and systemic embolism, whereas the primary safety endpoint was major bleeding. A meta-analysis of the trials [34] reveals that the NOACs significantly reduced the rate of stroke and systemic embolism by 19% (RR 0.81, 95% CI 0.73 to 0.91) mainly driven by a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38 to 0.64). Compared with warfarin, NOACs also significantly reduced all-cause mortality by 10% (RR 0.90, 95% CI 0.85 to 0.95) and intracranial hemorrhage by 52% (RR 0.48, 95% CI 0.39 to 0.59). With the exception of apixaban, however, the NOACs were associated with a 25% increase in the risk of gastrointestinal bleeding (RR 1.25, 95% CI 1.01 to 1.55). Therefore, the NOACs are at least as effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation and are associated with less intracranial hemorrhage and reduced all-cause mortality. Based on these observations, several recent guidelines give preference to the NOACs over warfarin for most patients with atrial fibrillation [35–37]. Certainly, the NOACs are more convenient to administer than warfarin and appear to be more cost-effective [38]. Consequently, they have the potential to increase the uptake of anticoagulation therapy for eligible patients with atrial fibrillation.

Potential limitations of the new oral anticoagulants

The lack of specific antidotes for the NOACs can complicate their reversal in patients who require urgent surgery or in those with life-threatening bleeding, a concern that makes some clinicians hesitant to prescribe the NOACs. Despite the lack of antidotes, however, the outcome in patients with intracranial bleeds or major bleeds in other sites was no worse in patients taking dabigatran than in those taking warfarin, and intracranial bleeding was less frequent with dabigatran than with warfarin [39,40]. Length of stay in the intensive care unit in patients who experienced a major bleeding event also was shorter in those taking dabigatran than in those on warfarin [40]. Similar results have been reported with rivaroxaban; in patients with intracranial bleeds, all-cause mortality was no different with rivaroxaban than with warfarin, and the same was true with major bleeding in other sites [41]. In patients requiring urgent surgery or interventions, the shorter half-lives of the NOACs relative to warfarin may be an advantage because there was less bleeding in such patients with dabigatran than with warfarin [42]. Emerging post-marketing data, primarily with dabigatran, suggest that the safety of the NOACs in the real world is similar to that observed in the trials [43]. Nonetheless, antidotes for dabigatran and the oral factor Xa inhibitors are under development, which will simplify the reversal of NOACs in emergency situations [44,45].

In the absence of laboratory monitoring, adherence may be more difficult to assess with the NOACs than with warfarin. Ongoing education and vigilance by physicians, nurses, and pharmacists can help to ensure adherence, and there is evidence that persistence with therapy may be better with NOACs than with warfarin [46].

Although routine monitoring is unnecessary, there are situations when the anticoagulant activity of the NOACs requires assessment. This can be complicated because the NOACs have variable effects on global tests of coagulation, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), depending on the reagent used for the assays [47]. Apixaban is particularly problematic because neither the PT nor the aPTT is responsive to its anticoagulant effects. Using drug-specific calibrators, the Hemoclot dilute thrombin time assay (Aniara Diagnostica, West Chester, OH) and chromogenic ecarin assay (Stago, Parsippany, NJ) have been developed to measure plasma dabigatran concentrations, whereas chromogenic anti-factor Xa assays can be used to measure the plasma concentrations of rivaroxaban, apixaban, or edoxaban, provided that drug-specific calibrators are available.

Not all patients are candidates for NOACs. For example, patients with mechanical heart valves should not be prescribed NOACs, because there was a trend for an increased risk of stroke and bleeding with dabigatran when it was compared with warfarin in such patients [48]. NOACs are also contraindicated in pregnant women and nursing mothers because, as small molecules, NOACs have the potential to pass through the placenta or to be excreted in breast milk. More information is needed about the use of NOACs in special populations, such as the morbidly obese, those of very low body weight, infants and children, and patients with antiphospholipid syndrome or other high-risk thrombophilic conditions.

Finally, though cheaper than LMWH, the NOACs are more expensive than warfarin. However, the cost is likely to decrease when all four agents are licensed for this indication, and with a reduced risk of bleeding compared with conventional therapy, the NOACs provide a cost-effective alternative to warfarin in patients with atrial fibrillation [38] and to LMWH in those undergoing hip or knee arthroplasty [15]. More work is needed to determine the cost-effectiveness of the NOACs for the treatment of VTE.

Conclusions and future directions

The NOACs represent a major advance in long-term anticoagulation therapy. Designed to be given in fixed doses without laboratory monitoring, the NOACs are easier to administer than warfarin. NOACs are at least as effective and safe as enoxaparin for thromboprophylaxis after elective hip or knee arthroplasty. For the treatment of acute VTE or for stroke prevention in atrial fibrillation, the NOACs are at least as effective as warfarin but are associated with less hemorrhage. Therefore, the benefit-to-risk profiles of the NOACs are superior to that of warfarin. The recommended doses for the NOACs in each of the licensed indications are outlined in Table 2.

Appropriate patient selection is critical for optimal use of the NOACs. NOACs, particularly dabigatran, should be used with caution in patients with a creatinine clearance of less than 30 mL/min, and NOACs should not be used in those with a creatinine clearance of below 15 mL/min. In patients started on a NOAC, follow-up is needed to monitor renal function, particularly in those with impaired kidney function at baseline, and to ensure adherence. The introduction of rapid assays to determine the plasma levels of the NOACs and antidotes to reverse their anticoagulant activity will simplify management of patients with serious bleeding or those who require urgent surgery or interventions. In the future, such assays may also help to tailor doses for patients with renal impairment. Therefore, management of NOACs is likely

to improve in the near future. In summary, NOACs have many benefits over warfarin and, within their licensed indications, provide an attractive alternative for many patients.

Abbreviations

AMPLIFY, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy; AMPLIFY-EXTENSION, Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy – Extended Treatment; aPTT, activated atrial thromboplastin time; CI, confidence interval; DVT, deep-vein thrombosis; EINSTEIN-DVT, Oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis; EINSTEIN-EXTENSION, Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism; EINSTEIN-PE, Oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic pulmonary embolism; Hokusai-VTE, Comparative Investigation of Low Molecular Weight Heparin/Edoxaban Tosylate Versus Low Molecular Weight Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, new oral anticoagulant; PCC, prothrombin complex concentrate; PE, pulmonary embolism; PT, prothrombin time; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6-Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etxilate versus Warfarin for 6-month Treatment for Acute Symptomatic Venous Thromboembolism; RE-MEDY, A Phase III, Randomised, Multicenter, Double-blind, Parallel-group, Active Controlled Study to Evaluate the Efficacy and Safety of Oral Dabigatran Etxilate (150 mg Bid) Compared to Warfarin (INR 2.0-3.0) for the Secondary Prevention of Venous Thromboembolism; RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long-Term Prevention of Recurrent Symptomatic; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Disclosures

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