Update on Anticoagulation: What the Interventional Radiologist Needs to Know

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Abstract

Keywords

- anticoagulants
- dabigatran
- rivaroxaban
- apixaban
- edoxaban
- interventional radiology

The novel oral anticoagulants (NOACs) represent a major advance in the treatment of patients with nonvalvular atrial fibrillation and venous thromboembolism (VTE). They have several advantages over vitamin-K antagonists such as warfarin, including more predictable pharmacokinetics and improved safety, particularly with fatal bleeding and intracranial hemorrhage. However, several issues remain surrounding the use of NOACs in certain subpopulations and with the approach to reversal. The periprocedural management of anticoagulation with these relatively new agents can also present several challenges. This article reviews the basic pharmacology, efficacy, and safety of these drugs. Several populations at higher risk for complications with use of NOACs are discussed, including those undergoing procedures. Finally, several target-specific reversal agents have either received FDA approval or likely will be approved in the near future; these agents and their roles in the approach to anticoagulation reversal will also be discussed.

Objectives: Upon completion of this article, the reader will be able to describe the pharmacology, indications, and safety of the novel oral anticoagulants (NOACs).

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While vitamin-K antagonists (VKAs) such as warfarin continue to be reliable choices for oral anticoagulation, several novel oral anticoagulants (NOACs) are now on the market in the United States and worldwide. Many are direct factor Xa inhibitors, including rivaroxaban (Xarelto, Bayer, Leverkusen, Germany),

apixaban (Eliquis, Bristol-Myers Squibb, New York, NY), and edoxaban (Savaysa, Lixiana Daiichi Sankyo, Tokyo, Japan).¹ Betrixaban (Portola Pharmaceuticals, South San Francisco, CA) is currently not approved by the Food and Drug Administration (FDA) for any indication, but is being studied for venous thromboembolism (VTE) prophylaxis in hospitalized patients (APEX study).² The NOACs also include dabigatran, an oral direct thrombin inhibitor with similar mechanism to argatroban, the latter being a parenteral agent mainly used in the treatment of heparin-induced thrombocytopenia.³ These targeted anticoagulants have several advantages over VKAs, but there are also several issues to consider with their use. In this article, these challenges and ways in which they can be addressed will be discussed.

General Pharmacology

The basic pharmacologic features of the NOACs are summarized in ►**Table 1**. VKAs such as warfarin exert their anticoagulant effect through prevention of posttranslational modification of the key procoagulant factors II (thrombin),

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Table 1 Pharmacologic characteristics of the NOACs

Target	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
	Thrombin	Xa	Xa	Xa	Xa
Peak activity (h)	2–3	3	3	1–2	3–4
Half-life (h)	12–17	5–9	9–14	10	20
Protein binding (%)	35	92–95	87	55	60
Metabolism	Glucuronidation (<10%)	CYP3A4 > CYP2J2	CYP3A4/5 > CYP21A2	P-glycoprotein > CYP3A4/5	P-glycoprotein
Bioavailability (%)	6	80	>50	62	34
Renal excretion (%)	80	66	~25	~50	17
Hepatic clearance (%)	~20	~28	~75	~50	~80

Abbreviations: CYP, cytochrome P-450; NOAC, novel oral anticoagulant.

VII, IX, and X, reducing their functional activity. The anticoagulant proteins C and S are also adversely affected. The broad impact of the VKAs helps explain their narrow therapeutic window. In contrast, each NOAC has a specific target in the coagulation cascade.⁴ Dabigatran targets thrombin, while rivaroxaban, apixaban, edoxaban, and betrixaban all target factor Xa.^{5,6} Unlike unfractionated heparin, fondaparinux, and the low-molecular-weight heparins (LMWH), which exert their effect through accentuating the endogenous anticoagulant activity of antithrombin, the NOAC Xa inhibitors do so directly. Compared with warfarin, NOACs achieve their anticoagulation effect much more quickly, but they vary in their half-lives and other pharmacokinetic parameters.

Betrixaban and dabigatran have the longest half-lives, while rivaroxaban has the shortest.^{2,7} Both dabigatran and rivaroxaban are mainly cleared via the kidneys, while apixaban and betrixaban are more dependent on hepatobiliary clearance. Rivaroxaban and apixaban are metabolized via the cytochrome P450 system, whereas edoxaban and betrixaban are primarily substrates of P-glycoprotein. Strong pathway inhibitors, such as clarithromycin, erythromycin, omega-3 fatty acids, and vitamin E, all may increase drug concentration and thereby the anticoagulant effect of rivaroxaban. This may also occur with concomitant use of omega-3 fatty acids and/or vitamin E with apixaban. Conversely, azole antimycotics and HIV protease inhibitors might reduce the effects of both rivaroxaban and apixaban.^{1,2,7,8}

Dabigatran is unique in having very low bioavailability and pH-dependent absorption, requiring formulation with tartaric acid.⁵ As such, the use of proton pump inhibitors and/or other antacids may reduce absorption of dabigatran.⁷

Owing to their rapid onset of action and accelerated clearance, the NOACs also have some advantages over warfarin for periprocedural management of anticoagulation, assuming adequate renal function. Regarding the use of VKA, whether to interrupt anticoagulation and for how long should weigh the risk of bleeding with the risk of thrombotic complications.^{9–11} Low-risk procedures (e.g., minor dental, dermatologic, ophthalmologic) do not routinely require interruption of anticoagulation. The procedure should be timed for the next dosing interval when drug concentration should be at its trough.¹¹ For procedures with a moderate or high risk of bleeding, each of the NOACs

varies to some degree on duration of interruption of anticoagulation. Rivaroxaban and edoxaban should be held for at least 24 hours prior to both moderate- and high-risk procedures. For dabigatran and apixaban, anticoagulation should be held for at least 24 hours prior to moderate-risk procedures and 48 hours prior to high-risk procedures.^{10,11}

Renal impairment delays clearance of NOACs, which can require a longer interruption of anticoagulation prior to procedures. Dabigatran is most affected because it is most dependent on renal excretion and also has the longest half-life. If creatinine clearance is less than 50 mL/minute, dabigatran should be held for at least 3 days prior to a procedure. This should be extended to a minimum of 5 days if creatinine clearance is less than 30 mL/minute. For rivaroxaban, apixaban, and edoxaban, patients with creatinine clearance less than 50 mL/minute should stop anticoagulation at least 2 to 3 days prior to moderate- or high-risk procedures.^{10,11}

The short time to achieve steady state and rapid clearance of NOACs make bridging anticoagulation with LMWH unnecessary under most circumstances.¹⁰ Bridging is mainly considered when interruption of anticoagulation is expected to be longer than 96 hours and in patients with a high risk of thrombotic complications. Use of either LMWH or unfractionated heparin may be needed in patients with renal or hepatic impairment on an agent with a longer half-life such as dabigatran, which could require cessation of the drug 5 days prior to a higher-risk procedure such as an abdominal surgery.^{9,11}

For all NOACs with an FDA indication at present, the manufacturers' recommendations state to restart the drug once hemostasis is achieved. In general, resuming anticoagulation should be delayed to at least 24 hours after procedures with a low risk of bleeding and to 48 to 72 hours after procedures with a moderate or high bleeding risk. There have been several reports of spinal punctures in anticoagulated patients leading to spinal hematomas and neurological compromise, especially with rivaroxaban and dabigatran.^{11,12} As a result, all of the NOACs have box warnings on their labels and specific recommendations regarding when to resume anticoagulation after spinal puncture, with or without epidural catheter placement. After a simple spinal puncture, dabigatran and edoxaban should be held for at least 2 hours. The recommendation for apixaban is for a 4-hour

delay in this setting, while rivaroxaban requires a 6-hour delay.^{9–12} These recommendations should always be considered within the context of each patient's risk of bleeding and thrombosis, and tailored accordingly.

General Indications, Efficacy, and Safety

Nonvalvular Atrial Fibrillation

All of the NOACs except betrixaban have been studied in large phase III clinical trials for prevention of stroke and systemic embolic events.^{13–16} A summary of the results of these studies is presented in ►Table 2. All were found to be noninferior to warfarin for the primary end point of stroke and systemic embolism prevention. Both dabigatran (150 mg BID) and apixaban (5 mg BID) showed a statistically significant reduction in risk of stroke and systemic

embolization.^{13,14} In the case of apixaban, the pivotal trial also met the key secondary outcome of reduced rate of death from any cause, which reached statistical significance.¹⁴

Initial Treatment of Venous Thromboembolism

Six large phase III clinical trials that included more than 27,000 patients compared the use of NOACs with standard VKA therapy in the initial treatment of acute VTE.^{17–22} The studies varied to some degree in the administration of the NOAC. For dabigatran and edoxaban, an initial overlap period of bridging with parenteral LMWH or unfractionated heparin was used in both the VKA and study drug groups. No overlap was used in those randomized to rivaroxaban or apixaban in the EINSTEIN or AMPLIFY studies, respectively. The duration of therapy also varied in these studies. For dabigatran and apixaban, patients were treated for 6 months, while in the

Table 2 Phase III clinical trials of NOACs for treatment and prophylaxis of thromboembolism

Clinical indication			
Nonvalvular atrial fibrillation	NOAC, n/N	Warfarin, n/N	Relative Risk Thrombus (95% CI)
<i>Prevention of stroke and systemic embolism</i>			
Dabigatran (RE-LY)	134/6,076	199/6,022	0.66 (0.53–0.82)
Rivaroxaban (ROCKET-AF)	269/7,081	306/7,090	0.88 (0.75–1.03)
Apixaban (ARISTOTLE)	212/9,120	265/9,081	0.80 (0.67–0.95)
Edoxaban (ENGAGE-AF)	296/7,035	337/7,036	0.88 (0.75–1.02)
Pooled	911/29,312	1,107/29,229	0.81 (0.73–0.91)
Initial treatment of VTE	NOAC	Standard therapy	Relative risk (95% CI)
<i>Recurrent VTE</i>			
Dabigatran (RE-COVER I–II)	60/2,574	55/2,579	1.09 (0.76–1.57)
Rivaroxaban (EINSTEIN DVT and PE)	86/4,151	95/4,131	0.89 (0.56–1.43)
Apixaban (AMPLIFY)	59/2,693	71/2,707	0.84 (0.59–1.17)
Edoxaban (HOKUSAI VTE)	130/4,143	146/4,149	0.89 (0.71–1.12)
Pooled	335/13,561	367/13,566	0.91 (0.79–1.06)
Extended treatment of VTE	NOAC	Placebo	Relative risk (95% CI)
<i>Recurrent VTE</i>			
Dabigatran (RE-SONATE)	3/681	37/662	0.08 (0.02–0.25)
Rivaroxaban (EINSTEIN-extension)	8/602	42/595	0.19 (0.09–0.40)
Apixaban (AMPLIFY-EXT)	66/1,657	96/829	0.34 (0.25–0.47)
Pooled	77/2,940	175/2,086	0.20 (0.09–0.44)
VTE prophylaxis after TKR or THR	NOAC	LMWH	Relative risk (95% CI)
<i>Symptomatic VTE</i>			
Dabigatran (RE-MODEL, RE-MOBILIZE, RE-NOVATE)	48/6,508	29/3,756	0.71 (0.23–2.12)
Rivaroxaban (RECORD 1–4, ODIXa trials)	32/6,828	71/6,936	0.48 (0.31–0.75)
Apixaban (ADVANCE I–III)	32/6,145	33/5,976	0.82 (0.41–1.64)
Pooled	112/19,481	133/16,668	0.65 (0.43–0.99)

Abbreviations: CI, confidence interval; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

Notes: Bold text highlights the indication for treatment. Italic text indicates the measured outcome in the studies and drug names (trial acronyms) have been listed under it. In the second and third columns, “n” refers to total number of events of the outcome that occurred. The “N” indicates the total number of patients in that study arm.

studies with rivaroxaban and edoxaban, 3, 6, or 12 months of therapy were used at the discretion of the treating physician. Each of the studies established noninferiority to therapy with VKAs for the primary efficacy end point, while none of the studies were shown to be superior.

A pooled meta-analysis of all six phase III studies reported a rate of recurrent VTE of 2.0% in patients receiving NOACs versus 2.2% in VKA-treated patients, without significant study heterogeneity.²³ Another meta-analysis of the same six studies confirmed these findings, showing a relative risk (RR) for recurrent VTE of 0.91 (95% confidence interval [CI]: 0.79–1.06) in patients receiving NOACs versus VKAs.²⁴ These findings were consistent across age and gender and in subgroups of patients with pulmonary embolism, renal impairment, and those with cancer, though many of these subgroups were small due to lack of enrollment or study exclusion criteria.^{8,24}

Extended Treatment of Venous Thromboembolism

There have been several studies evaluating NOACs for extended duration of therapy following primary treatment in VTE.^{25–27} A meta-analysis of four studies including nearly 8,000 patients showed a reduced rate of recurrent VTE (RR: 0.20, 95% CI: 0.09–0.44) in those who continued NOAC therapy compared with placebo. This was associated with an increased risk of clinically relevant bleeding, defined as a composite of major bleeding and clinically significant non-major bleeding (RR: 2.61, 95% CI: 1.24–5.50).²⁸ Dabigatran has also been shown to be noninferior to warfarin in the prevention of recurrent VTE in this setting, with a slightly lower bleeding risk.²⁷

Venous Thromboembolism Prophylaxis after Total Hip or Knee Replacement

Dabigatran, rivaroxaban, and apixaban have all been studied for use for VTE prophylaxis after total hip (THR) or total knee replacement (TKR).²⁹ Dabigatran 220 mg once daily was shown to be noninferior to enoxaparin for prevention of symptomatic VTE, with a similar risk for clinically relevant bleeding.^{30,31} Rivaroxaban 10 mg once daily showed a reduced rate of symptomatic VTE versus enoxaparin, but

this was offset by an increased risk of clinically relevant bleeding (RR: 1.25, 95% CI: 1.05–1.49).^{32,33} Similar rates of symptomatic VTE were noted with apixaban 2.5 mg BID and prophylactic enoxaparin post-THR and TKR, although there was a small but statistically significant reduction in clinically relevant bleeding associated with apixaban.^{34,35} The recommended time for initiation of anticoagulation varies between agents: dabigatran can be started 1 to 4 hours postoperatively as a one-time 110-mg dose, rivaroxaban should be started 6 to 10 hours postoperatively, and apixaban should be started 12 to 24 hours postoperatively. In general, anticoagulation is continued for a minimum of 10 to 14 days, which can be extended to 35 days depending on bleeding and thrombosis risk.²⁹ Edoxaban is currently being evaluated in the THR and TKR settings, but is currently not approved by the FDA for these indications.

Bleeding Risk

Bleeding complications present a significant challenge in the use of anticoagulation, as many thrombotic risk factors are also associated with an increased risk of bleeding. Long-term anticoagulation with VKAs is associated with approximately 1 to 3 major bleeding events per 100 patient-years, but can be as much as 6.5% per year in patients at higher risk for bleeding.^{36,37} As shown in ▶Table 3, major bleeding rates with the use of NOACs are comparable and often lower than with use of warfarin. A meta-analysis of the six large studies of NOACs for acute treatment of VTE demonstrated a statistically significant reduction in major bleeding (RR: 0.61, 95% CI: 0.45–0.83), fatal bleeding (RR: 0.36, 95% CI: 0.15–0.84), intracranial hemorrhage (RR: 0.37, 95% CI: 0.21–0.68), and clinically relevant non-major bleeding (RR: 0.73, 95% CI: 0.58–0.93).²³

In nonvalvular atrial fibrillation, the most important risk reduction was seen in the incidence of intracranial hemorrhage.^{13–16} A potential explanation is that the brain has higher levels of tissue factor and may be more susceptible to bleeding caused by disruption of the extrinsic pathway from reduced levels of factor VIIa in patients using VKAs. In the setting of extended duration of anticoagulation, rates of

Table 3 Major bleeding with NOACs versus warfarin

	Atrial fibrillation	Acute VTE	Extended VTE	Post TKR/THR prophylaxis
Dabigatran	150 mg BID: RR 0.93 (0.81–1.07)	HR 0.82 (0.45–1.48)	vs. warfarin: RR 0.52 (0.27–1.02)	HR 1.12 (0.94–1.35)
	110 mg BID: RR 0.80 (0.69–0.93)	–	vs. placebo ^a : RR 2.92 (1.52–5.60)	–
Rivaroxaban	HR 1.04 (0.90–1.20)	HR 0.49 (0.31–0.79)	vs. placebo ^a : RR 5.19 (2.3–11.7)	HR 1.25 (1.05–1.49)
Apixaban	HR 0.69 (0.60–0.80)	HR 0.30 (0.17–0.55)	5 mg vs. placebo 0.25 (0.03–2.24)	HR 0.82 (0.69–0.98)
Edoxaban	HR 0.47 (0.41–0.55)	HR 0.84 (0.59–1.21)	2.5 mg vs. placebo 0.49 (0.09–2.64)	–
Pooled	HR 0.86 (0.73–1.00)	HR 0.62 (0.45–0.85)	–	HR 1.06 (0.92–1.22)

Abbreviations: BID, twice a day; HR, hazard ratio; NOAC, novel oral anticoagulant; RR, relative risk; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

^aMajor or clinically relevant non-major bleeding.

bleeding were expectedly higher for dabigatran and rivaroxaban when compared with placebo. For dabigatran, major and clinically relevant non-major bleeding risk was lower compared with extended therapy with warfarin (RR: 0.54, 95% CI: 0.41–0.71).^{26,27} Interestingly, when apixaban was compared with placebo for extended treatment of VTE, bleeding rates were comparable at both the 2.5- and 5-mg doses.²⁵

In aggregate, bleeding rates with NOACs are lower than with VKAs in several major categories. A meta-analysis of 12 randomized studies including more than 100,000 patients showed a statistically significant reduction in major bleeding (RR: 0.72, 95% CI: 0.62–0.85), fatal bleeding (RR: 0.53, 95% CI: 0.43–0.64), intracranial bleeding (RR: 0.43, 95% CI: 0.37–0.50), clinically relevant non-major bleeding (RR: 0.78, 95% CI: 0.68–0.90), and total bleeding (RR: 0.76, 95% CI: 0.71–0.82) with use of NOACs versus VKA. Gastrointestinal bleeding events were statistically comparable between the NOACs and VKA use.³⁸ However, a higher rate of gastrointestinal bleeding was seen with dabigatran versus warfarin in the RE-LY study for nonvalvular atrial fibrillation at the 150-mg BID dose (1.6 vs. 1.1/100 patient-years).¹³

Clinical Experience with the NOACs

As previously outlined, the safety profiles for all of the NOACs have been excellent in their respective clinical trials. However, as with all new drugs, actual clinical experience can vary from study results. After some early concerns, the safety profile of the NOACs has been favorable as more patients receive these drugs outside the clinical trial setting.

Based on the RE-LY study's aforementioned safety findings, there was potential concern for higher rates of gastrointestinal bleeding following FDA approval of dabigatran in October 2010. Initially, there was a higher-than-expected rate of gastrointestinal bleeding with general use, even when compared with the rate seen in the RE-LY study population.¹³ However, continued surveillance and accumulation of data from October 2010 to December 2011 demonstrated overall bleeding rates to be equal or slightly lower with dabigatran. Analysis of more than 100,000 patient-days showed lower rates of gastrointestinal bleeding (1.6 vs. 3.5%) and intracranial hemorrhage (0.8 vs. 2.4%) with the use of dabigatran versus warfarin, respectively. It is possible that hypervigilance for adverse effects soon after the FDA approval of dabigatran led to the initial increase in observed bleeding events.¹

Another recent study evaluated the use of rivaroxaban in 1,700 patients in general practice. In over 2 years of experience, 43% of patients on rivaroxaban experienced a total of 1,082 bleeding events. Of those, 59% were considered minor and only 6% were considered major. By indication, major bleeding rates were 3.1 per 100 patient-years for use in atrial fibrillation and 4.1 per 100 patient-years for use in VTE treatment. Case fatality rates were 5.1 and 6.3% at 30 and 90 days, respectively.³⁹ When compared with the use of VKAs in actual clinical practice, rivaroxaban has at least comparable and likely better rates of both major and fatal bleeding.

Special Populations

The more reliable pharmacokinetics of the NOACs obviate the need for routine laboratory monitoring, but there are several patient populations in which concern for inadequate anticoagulation, or conversely higher bleeding risk, may be raised with the use of NOACs at standard, fixed dosing. Several of these populations are discussed later.

Renal Impairment

As demonstrated in ▶ **Table 1**, the NOACs vary significantly in their degree of renal clearance. Dabigatran is the most dependent on renal function (80% renal clearance), whereas apixaban and betrixaban are much less so (25 and 17%, respectively). While all of the major phase III studies excluded patients with severe renal dysfunction (glomerular filtration rate (GFR) < 30 mL/min), they did include a significant number of patients with moderate renal impairment (GFR between 30 and 49 mL/min).^{1,8} Overall, the NOACs were equally effective to slightly more effective than VKAs in the prevention of stroke and systemic embolization in patients with moderate renal impairment and nonvalvular atrial fibrillation. Rates of stroke and systemic embolization were higher in rivaroxaban-treated patients with atrial fibrillation and moderate renal impairment compared with those on rivaroxaban with creatinine clearance more than 50 mL/minute (2.32 vs. 1.57 events/100 patient-years), but those rates were not higher than in VKA-treated patients with moderate renal impairment or with normal creatinine clearance.^{8,40} Similarly, NOACs were still as effective as VKAs in the treatment of VTE in patients with moderate renal dysfunction. For this indication, a statistically significant reduction in major bleeding was also observed (RR: 0.51, 95% CI: 0.26–0.99).²³ It is important to note that dose reductions were used in this study for rivaroxaban, apixaban, and edoxaban.⁴⁰

Interestingly, a higher rate of ischemic stroke was observed in patients on edoxaban for nonvalvular atrial fibrillation with creatinine clearance more than 95 mL/minute. Post hoc analyses of the original phase III data suggest this is related to reduced plasma concentrations of edoxaban in these patients.⁴⁰

Dosing recommendations for patients with severe renal impairment are available for the NOACs, but caution should be used in this population, as the phase III studies for these agents excluded patients with creatinine clearance less than 30 mL/minute. More data are needed to determine the safety of the use of NOACs in patients with severe renal impairment. Validated monitoring assays would also significantly improve the safety profile in this population.¹

Extremes of Weight

There are no specific dosing adjustments or specific recommendations in obese patients for any of the NOACs, but it is still unclear if one standard dose is adequate for a patient weighing ≥150 kg versus a patient with a weight of 70 kg. The phase III randomized studies of the NOACs did not have exclusion criteria based on weight, and the number of obese patients included in each study varied significantly. For example, the AMPLIFY study of apixaban for VTE treatment included 522 patients with weight

≥ 100 kg, which was nearly 20% of the total study population. In the EINSTEIN studies (rivaroxaban), more than 14% of patients weighed ≥ 100 kg, and more than 3,000 patients weighed ≥ 100 kg on dabigatran in RE-LY. Each study showed no effect of high body weight on efficacy or safety of each of the NOACs.^{13,19–21} A meta-analysis by van Es et al confirmed these findings.²³ It is important to note, however, that there were very few patients whose weights were more than 120 kg in any of the clinical trials.

Patients with low body weight should also be given special consideration, as they may be at higher risk for bleeding. Again, these patients were not excluded from the phase III studies, but they were represented in relatively small numbers. The ARISTOTLE trial of apixaban use in nonvalvular atrial fibrillation included the largest number, with nearly 2,000 patients at ≤ 60 kg. The ENGAGE-AF trial of edoxaban in nonvalvular atrial fibrillation included more than 1,300 patients at this weight. Data generated from ARISTOTLE resulted in recommendations for a reduced dose of apixaban at 2.5 mg twice daily in patients meeting two of the following criteria: body weight ≤ 60 kg, age ≥ 80 years, or creatinine ≥ 1.5 mg/dL. Similarly, the dose of edoxaban should be reduced by 50% in patients with body weight ≤ 60 kg.^{14,16,40} Dabigatran and rivaroxaban do not currently require dose adjustment for weight.

Age

Older patients are at higher risk for both thrombosis and bleeding because of several factors, including variable renal function or impairment, polypharmacy, and more comorbidities. Nevertheless, the data on the use of NOACs in this population show they are either comparable to or better than VKAs in both safety and efficacy. A meta-analysis of 10 studies of dabigatran, rivaroxaban, and apixaban that included more than 25,000 patients showed no difference in rates of major or clinically significant non-major bleeding with the NOACs compared with VKAs (odds ratio: 1.02). The same meta-analysis showed that the NOACs were more effective in the prevention of stroke and systemic embolization in atrial fibrillation, as well as reducing recurrent thrombosis when used in the treatment of acute VTE.⁴¹ Another pooled analysis of the phase III studies for acute VTE treatment showed a statistically significant reduction in VTE recurrence with NOACs compared with warfarin in patients ≥ 75 years of age (RR: 0.56, 95% CI: 0.38–0.82). The rate of major bleeding was also statistically lower with the NOACs (RR: 0.49, 95% CI: 0.25–0.96).²³

The phase III studies of dabigatran showed a trend toward higher rates of bleeding in older patients at both the 110- and 150-mg doses. Treatment by age interaction was statistically significant. The direct factor Xa inhibitors did not show this effect. Dabigatran is more dependent on renal clearance compared with the factor Xa inhibitors and, as a result, may not be cleared as effectively in older patients.⁷ Despite the observed trend, bleeding rates with dabigatran use were still comparable to VKA use, and importantly, rates of intracranial hemorrhage were still lower with dabigatran compared with warfarin.⁴²

Cancer

Active malignancy is a well-known risk factor for incident and recurrent VTE. Management of anticoagulation in the cancer population can be especially challenging in the setting of intermittent myelosuppressive chemotherapy. The CLOT study demonstrated a statistically significant reduction in recurrent VTE with use of LMWH compared with warfarin, and therefore LMWH continues to be standard of care in this population.^{37,43} The phase III studies of NOACs in VTE used either VKAs or placebo and not LMWH in their control arms. They also included relatively few patients with cancer, ranging from approximately 3% in the AMPLIFY study to 10% in the HOKUSAI-VTE study.^{21,22} Data on the type of malignancy, stage, and chemotherapy use were not available, all of which impact thrombotic risk.

A meta-analysis of the six phase III studies of NOACs used for acute VTE treatment found a total of 1,581 patients with active malignancy. In this pooled group, the authors reported a statistically significant reduction in the risk of recurrent thrombosis with NOAC use versus VKA use (3.4 vs. 5.9%, RR: 0.57, 95% CI: 0.36–0.91). Rates of major bleeding were comparable between the two groups (2.9 vs. 3.7%, RR: 0.77, 95% CI: 0.44–1.33). However, bleeding rates were higher in the cancer population compared with noncancer patients for both VKAs and NOACs.²³ Again, specifics of key features of malignancy were not reported.

These results suggest that the NOACs are likely effective in the cancer population, but a direct comparison to LMWH is necessary to potentially change the standard of care for malignancy-associated thrombosis. Clarification of cancer type, stage, and treatment modalities to fully investigate safety and efficacy will hopefully better delineate which patients may best be treated with a NOAC in this population. Clinical trials comparing the factor Xa inhibitors to LMWH are ongoing for rivaroxaban (NCT02583191), apixaban (NCT00643201, NCT02585713), and edoxaban (NCT02073682).

Massive or Submassive Pulmonary Emboli

Patients presenting with massive or submassive pulmonary emboli were largely excluded from the phase III studies with NOACs. However, the Hokusai study did enroll 938 patients with pulmonary emboli associated with right ventricular dysfunction, but this was defined by elevation of N-terminal pro-brain natriuretic peptide.²² In this subgroup, recurrent VTE was lower in those patients treated with edoxaban (3.3%) versus VKA (6.2%), which did meet statistical significance. However, this study excluded patients with more unstable pulmonary emboli that may have required thrombectomy, thrombolytic therapy, or insertion of an inferior caval filter, as did those studies evaluating dabigatran, rivaroxaban, and apixaban.^{17,20,21} From a mechanistic standpoint, there is no reason to believe that any of these agents would not be options for continued therapy once the patient has been stabilized and completed current protocols for systemic or catheter-directed thrombolytic therapy.

Reversal

Patients on NOACs may require urgent or nonurgent reversal of anticoagulation for many reasons such as acute bleeding, traumatic injury, or emergent invasive procedures. Less urgent reversal may be necessary with acute impairment of renal or hepatic function causing decreased clearance of the drug. The introduction of new medications in addition to NOACs can cause drug-drug interactions or have an adverse effect on renal or hepatic function, causing increased anticoagulant activity.

For warfarin, the options for reversal are well established. Vitamin-K replacement is sufficient for correction of supra-therapeutic international normalized ratio (INR) without bleeding and for some minor bleeding. Vitamin K is available in oral, subcutaneous, and intravenous formulations. Rapid reversal of VKAs can be achieved with transfusion of fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC), which rapidly replace vitamin-K-dependent clotting factors (II, VII, IX, and X).

In the case of the NOACs, several clotting factor preparations are available with mixed results in terms of safety and efficacy. Hemodialysis remains an option for reversal of dabigatran, as the drug has minimal protein binding and is primarily excreted by the kidneys.^{44,45} Dialysis is not effective for removal of the direct Xa inhibitors. More target-specific reversing agents are either on the market or in the advanced stages of clinical trial development. Dabigatran now has an FDA-approved reversing agent, the monoclonal antibody idarucizumab (Praxbind, Boehringer Ingelheim, Ingelheim, Germany). For the factor Xa inhibitors, a class-wide agent, andexanet alfa (PRT4445, Portola Pharmaceuticals) has completed phase II clinical trials with promising results, and phase III studies are underway.

Prothrombin Complex Concentrates

There are two forms of PCC available, both of which are prepared from plasma. The three-factor PCC contains prothrombin (factor II), factor IX, and factor X, while the four-factor PCC contains the same three factors in addition to factor VII. These factors can be either activated or nonactivated. Both also naturally contain the anticoagulant proteins C and S, as well as antithrombin. The PCCs are advantageous over FFP in that they contain higher concentrations of the vitamin-K-dependent factors, are much smaller in volume and therefore less likely to cause circulatory overload, and are less likely to carry infectious agents.⁴⁶

Data are limited on the use of PCCs for reversal of the novel anticoagulants.⁴⁷ A small, randomized, double-blind, placebo-controlled study of 12 healthy young male volunteers given either rivaroxaban or dabigatran had mixed results. A nonactivated PCC reversed the anticoagulant effects of rivaroxaban based on correction of endogenous thrombin potential and prothrombin time. However, no improvement in thrombin time or Ecarin clotting time (ECT) was seen in dabigatran-treated patients.⁴⁸ In contrast, an animal model of trauma did show benefit of activated PCC in the reversal of dabigatran and cessation of

bleeding.⁴⁷ Data for the use of PCCs for reversal of apixaban or edoxaban are largely limited to animal models, in vitro studies, and case reports. It is also important to note that the activated PCCs carry an increased risk of thrombotic complications.^{46,47}

Idarucizumab

Idarucizumab is a monoclonal antibody fragment (Fab fragment) that binds to dabigatran with an affinity 350 times greater than that of thrombin. The resulting drug-Fab fragment complex has no activity on coagulation or platelet function. Unbound idarucizumab does not appear to increase the risk for thrombosis, as its intended target is dabigatran and not the coagulation cascade, which contrasts with that previously mentioned regarding PCC.⁴⁹ Idarucizumab received accelerated FDA approval in October 2015 for reversal of the anticoagulant effect of dabigatran prior to emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. The approval was based on three randomized, placebo-controlled trials enrolling a total of 283 healthy volunteers and an ongoing open-label, multicenter trial enrolling patients with life-threatening or uncontrolled bleeding or those needing emergency surgery/urgent procedures. The drug is administered via two 50-mL intravenous infusions or injections each containing 2.5 g of idarucizumab, given no more than 15 minutes apart.⁵⁰⁻⁵³

At the time of this writing, an interim analysis of 90 patients who received idarucizumab either for life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures is available. Of those enrolled, 51 patients had uncontrolled bleeding and 39 required reversal for an emergent procedure. The primary outcome was the percentage of anticoagulation reversed based on dilute thrombin time and ECT, two coagulation studies that have been shown to correlate well with plasma concentration of unbound dabigatran.⁵³

Of the patients with uncontrolled bleeding, 98% achieved a normal dilute thrombin time and 89% achieved a normal ECT; for those undergoing emergent procedures, 93% achieved a normal dilute thrombin time and 88% achieved a normal ECT. For all patients, a response was seen within minutes after the first infusion of idarucizumab.⁵³ While these early results are very promising, more data are needed from clinical trials as well as actual clinical practice to better understand the use of this drug.

Andexanet Alfa

Andexanet alfa is a recombinant human factor Xa decoy protein designed to neutralize both direct and indirect factor Xa inhibitors. It is modified in three locations rendering it catalytically inactive, but it maintains high affinity for the active binding site of factor Xa inhibitors.^{54,55} Phase II studies have been completed assessing reversal of all four of the direct factor Xa inhibitors with andexanet alfa. These studies showed reproducible, dose-dependent reversal of factor Xa inhibition, with no serious adverse events.^{55,56}

A randomized, placebo-controlled clinical trial assessing reversal of anticoagulation with andexanet alfa has also been

completed.⁵⁵ A total of 101 healthy volunteers between the age of 50 and 75 years receiving either rivaroxaban or apixaban were included. Andexanet was administered either as a one-time intravenous bolus or as a bolus with a 2-hour intravenous infusion. Anti-factor Xa activity was reduced by 94% for those on apixaban and by 92% for those on rivaroxaban. Thrombin generation was restored within normal limits in 100% of those receiving apixaban and 96% of those receiving rivaroxaban. The effect was seen within 2 to 10 minutes and was more prolonged with the additional continuous infusion versus the bolus alone. There were no serious adverse events or thrombotic complications.⁵⁵ Further studies evaluating the efficacy of andexanet alfa during life-threatening bleeding events or prior to emergent procedures are necessary to truly ascertain the drug's clinical value. Phase III studies of patients on edoxaban and betrixaban will also be helpful to ensure that andexanet alfa is effective for reversal of all of the oral factor Xa inhibitors.

Aripazine

Aripazine is a small, water-soluble molecule that has multiple binding sites, allowing it to interact with several anticoagulants. Through hydrogen bonding, it is able to bind to direct Xa inhibitors, unfractionated heparin and LMWH, fondaparinux, and thrombin inhibitors, including both argatroban and dabigatran. It has favorable pharmacologic properties, with rapid onset of action (~30 minutes), a short half-life (1.5 hours), no plasma protein binding, and little to no interaction with other medications. While currently in phase II clinical studies, to date it has shown promise in reversing anticoagulant effects of various drugs in animal models, with decreased bleeding in rat tail and rabbit liver laceration models.⁵⁷ Aripazine was also able to reverse the anticoagulant effects of edoxaban on 80 human volunteers, with rapid normalization of whole blood clotting times following administration.⁵⁸ Its broad activity against a spectrum of anticoagulants may make it an ideal antidote for those requiring reversal regardless of agent.

Conclusion

The NOACs have greatly expanded anticoagulant treatment options. They share several favorable features that improve upon previously available anticoagulants, including oral bioavailability, rapid onset of action, relatively short half-lives, and reproducible anticoagulant effect obviating the need for routine monitoring. As a group, they have been shown to be at least as effective as VKA in stroke prevention in atrial fibrillation, treatment of acute VTE, and for longer-term prevention of VTE recurrence. Safety is another advantage, with bleeding rates being comparable to somewhat lower than in VKA, particularly for fatal bleeding and intracranial hemorrhage. There is ongoing development of drug-specific reversal agents that do not carry significant prothrombotic risks; if successful, this will only add to the appeal of NOACs. Additional clinical data are needed to more fully evaluate

their potential role in specific patient populations, including malignancy-associated VTE.

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