

Evidence Gaps in the Era of Non–Vitamin K Oral Anticoagulants

Konstantinos N. Aronis, MD; Elaine M. Hylek, MD, MPH

Vitamin K antagonists (VKAs) were first introduced in the 1920s from studies on the “hemorrhagic” effect of spoiled sweet clover consumption by cattle¹ and have evolved ever since to the cornerstone of oral anticoagulation therapy. The most commonly used VKA in the United States is warfarin, while in some European countries acenocoumarol and phenprocoumon are commonly used.² VKAs exhibit their anticoagulant effect by inhibiting the vitamin K epoxide reductase complex subunit 1 in the liver. This enzyme catalyzes the post-translational modification of vitamin K–dependent proteins. Inhibition of vitamin K epoxide reductase complex subunit 1 results in impaired synthesis of coagulation factors II (prothrombin), VII, IX, and X as well as of anticoagulant proteins C, S, and Z.³ The primary indications for VKA use are prophylaxis and treatment of venous thromboembolic disease (VTE, which includes deep vein thrombosis and pulmonary embolism) and of thromboembolic complications associated with atrial fibrillation (AF) and/or mechanical cardiac valves.

Although VKAs are efficacious in the prevention and treatment of VTE⁴ and AF-related thromboembolic complications,⁵ their use has some hindrances. First, the dose required to provide therapeutic anticoagulation is highly variable between individuals. It is influenced by various pharmacogenetic parameters, such as polymorphisms affecting VKA pharmacokinetics (cytochrome *CYP2C9* gene that regulates VKAs hepatic metabolism)⁶ and pharmacodynamics (*VKORC1* gene).⁷ Second, co-administration of other medications, such as anti-inflammatory, antibiotics, antiplatelets, statins, antidepressants, amiodarone, antifungals,

antiretrovirals, and over-the-counter dietary supplements, can interact with VKAs.⁸ Third, changes in dietary patterns or alcohol consumption alter the efficacy of VKAs, requiring adjustment of the maintenance dose.⁸ Last, given this variability and the narrow therapeutic window of VKAs, frequent anticoagulation monitoring is required to ensure appropriate dosing.⁹

The need to overcome these limitations resulted in the development of a new class of oral anticoagulants, the non–vitamin K oral anticoagulants (NOACs), also known as “direct oral anticoagulants.” Currently, there are 5 NOACs that have completed phase III clinical trials and are approved for clinical use (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban). Contrary to VKAs that indirectly inhibit the synthesis of coagulation factors, NOACs directly inhibit specific coagulation factors. Dabigatran inhibits thrombin (factor IIa), whereas apixaban, betrixaban, edoxaban, and rivaroxaban inhibit activated factor X (Xa).¹⁰ These agents have more predictable pharmacokinetics and pharmacodynamics than VKAs and a wide therapeutic window, allowing for a fixed oral dosing, without the need for monitoring their anticoagulation effect. In addition, most have a short elimination half-life compared with VKAs and rapid onset of action, achieving therapeutic levels in the plasma within 1 to 2 hours.¹⁰ Betrixaban has distinct pharmacokinetic properties because it is minimally cleared by the liver and the kidneys and has a prolonged half-life.¹¹ The terminal half-life of betrixaban is 37 hours. Table 1 summarizes the landmark phase III clinical trials involving NOACs. These trials demonstrate noninferiority or superiority of NOACs compared with VKAs in stroke prevention in patients with AF,^{12–16} and prevention^{17–19} and treatment^{20–25} of VTE, with a better safety profile. The results from phase III clinical trials on NOACs and the ease of their use have resulted in their progressively increasing utilization. However, some areas of uncertainty remain. First, their efficacy has not been validated in patients with severe mitral stenosis or mechanical prosthetic valves. RE-ALIGN (A Randomised, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients After Heart Valve Replacement), a phase II clinical trial of dabigatran in patients with mechanical heart valves, was discontinued prematurely because of an increased rate of thromboembolic and bleeding events among patients in the dabigatran group.²⁶ Second, there are limited data in patients with cancer-associated VTE or other hypercoagulable

From the Division of Cardiology, Johns Hopkins Hospital, Johns Hopkins University School of Medicine, Baltimore, MD (K.N.A.); Section of General Internal Medicine, Boston Medical Center, Boston University School of Medicine, Boston, MA (E.M.H.).

Correspondence to: Konstantinos N. Aronis, MD, Division of Cardiology, Johns Hopkins Hospital, 1800 Orleans Street, Zayed 7125, Baltimore, MD 21287. E-mail: karonis1@jhmi.edu

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Table 1. Landmark Phase III Clinical Trials Demonstrating the Efficacy of NOACs in Thromboembolism Prophylaxis in Patients With AF and Management of VTE

Study	Agent	Year	Design	Relevant Exclusion Criteria	Results
AF					
RE-LY ¹²	Dabigatran	2009	Dabigatran (110 or 150 mg twice daily) vs dose-adjusted warfarin	Severe valvular heart disease or prosthetic valve, severe stroke within 6 mo, increased risk for hemorrhage, CrCl <30 mL/min, active liver disease and pregnancy	Dabigatran 110 mg: noninferior to warfarin with lower rate of ICH and other major hemorrhage Dabigatran 150 mg: superior to warfarin with lower rate of ICH, similar rate of other major hemorrhage
ROCKET AF ¹³	Rivaroxaban	2011	Rivaroxaban (20 mg/d) vs dose-adjusted warfarin	Hemodynamically significant mitral stenosis, prosthetic heart valve, severe, disabling stroke within 3 mo or any stroke within 14 d, active internal bleeding, major surgical procedure or trauma within 30 d of randomization, CrCl <30, pregnancy, known liver disease and severe comorbid condition with life expectancy ≤2 y	Rivaroxaban: noninferior to warfarin with lower rate of ICH, similar rate of other major hemorrhage
AVERROIS ¹⁴	Apixaban	2011	Apixaban (5 mg twice/d) vs aspirin (81–324 mg) in patients for whom VKA was unsuitable	Valvular disease requiring surgery, a serious bleeding event in the previous 6 mo or high risk of bleeding, stroke within the previous 10 d, life expectancy of <1 y, CrCl <25 mL/min and abnormal liver function	Apixaban: reduced risk of SSE without significantly increasing the risk of major bleeding or ICH
ARISTOTLE ¹⁵	Apixaban	2011	Apixaban (5 mg twice/d) vs dose-adjusted warfarin	Moderate or severe mitral valve stenosis, prosthetic, mechanical valve, stroke within 7 d, CrCl <25 mL/min, abnormal liver function tests, pregnancy, severe comorbid condition with life expectancy ≤1 y	Apixaban: superior to warfarin with lower rate of ICH and lower rate of other major hemorrhage
ENGAGE AF—TIMI 48 ¹⁶	Edoxaban	2013	Edoxaban (30 or 60 mg daily) vs dose-adjusted warfarin	Moderate-to severe mitral stenosis, CrCl <30 mL/min, a high risk of bleeding, acute coronary syndromes, coronary revascularization, or stroke within 30 d before randomization	Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes
Treatment of venous thromboembolic disease					
RE-COVER ²⁰	Dabigatran	2009	Comparison of dabigatran (150 mg twice/d) vs dose-adjusted warfarin in patients with acute VTE after a therapy for a median of 9 da with parenteral anticoagulation with the outcome or recurrent VTE and related mortality	Duration of symptoms longer than 14 d, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, a high risk of bleeding, liver disease, CrCl <30 mL/min, life expectancy <6 mo, pregnancy	Dabigatran is as effective as warfarin in preventing VTE recurrence and mortality and was associated with lower rates of any bleeding (but similar rates of major bleeding)

Continued

Table 1. Continued

Study	Agent	Year	Design	Relevant Exclusion Criteria	Results
RE-SONATE ²¹	Dabigatran	2013	Comparison of dabigatran (150 mg twice/d) vs placebo in patients with VTE who previously received anticoagulation for 6 to 18 mo, with the outcome of recurrent or fatal VTE	Active liver disease, CrCl <30 mL/min, acute bacterial endocarditis, active bleeding or high risk for bleeding, uncontrolled hypertension, life expectancy <6 mo, pregnancy	Dabigatran reduced recurrent symptomatic or fatal VTE significantly more compared with placebo but was associated with higher rates of major, clinically relevant or any bleeding
RE-MEDY ²¹	Dabigatran	2013	Comparison of dabigatran vs dose-adjusted warfarin in patients with VTE who had already received at least 3 mo of anticoagulation, with the outcome of recurrent or fatal VTE	Interruption of anticoagulant therapy for 2 or more wks during the 3 to 12 mo of treatment for the prior VTE, patients with an excessive risk of bleeding, abnormal liver function tests, CrCl <30 mL/min	Dabigatran reduced recurrent symptomatic or fatal VTEs at rates similar to warfarin and was associated with lower rate of major, clinically relevant and any bleeding
EINSTEIN-DVT ²²	Rivaroxaban	2010	Comparison of rivaroxaban alone (15 mg twice daily for 3 wks, followed by 20 mg once daily) vs enoxaparin followed by dose-adjusted VKA for 3, 6, or 12 mo in patients with acute, symptomatic DVT with the outcome or recurrent VTE	Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE	Rivaroxaban had similar effect to enoxaparin-warfarin in preventing recurrent VTE and had similar rates of major, or clinically relevant bleeding
EINSTEIN-PE ²³	Rivaroxaban	2012	Comparison of rivaroxaban alone (15 mg twice daily for 3 wks, followed by 20 mg once daily) vs enoxaparin followed by dose-adjusted VKA for 3, 6, or 12 mo in patients with acute, symptomatic PE with the outcome or recurrent symptomatic VTE	Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE	Rivaroxaban alone had similar effect to enoxaparin-warfarin in preventing recurrent VTE both for the initial and long-term treatment of pulmonary embolism and was associated with lower major bleeding rates
AMPLIFY ²⁴	Apixaban	2013	Comparison of apixaban (10 mg twice daily for 7 d, followed by 5 mg twice daily for 6 mo) with enoxaparin, followed by warfarin in patients with acute VTE with the outcome of recurrent symptomatic or fatal VTE	Hemoglobin level <9 mg/dL, platelet count <100 000/mm ³ , CrCl <25 mL/min, short life expectancy, active bleeding or high risk for serious bleeding	Apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with significantly less major and clinically relevant bleeding rates
Hokusai-VTE ²⁵	Edoxaban	2013	Comparison of edoxaban (60 mg once daily, or 30 mg once daily if CrCl 30–50 mL/min) vs dose-adjusted warfarin for 3 to 12 mo in patients with acute VTE who had initially received heparin, with the outcome of recurrent symptomatic VTE	Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE, CrCl <30 mL/min, significant liver disease, patients with active cancer for whom long-term treatment with low molecular weight heparin is anticipated, active bleeding or high risk for bleeding, chronic treatment with aspirin or nonsteroidal anti-inflammatory drugs, concurrent treatment with potent glycoprotein P inhibitors	Edoxaban administered once daily after initial treatment with heparin was noninferior to standard therapy and was associated with lower major or clinically relevant bleeding rates

Continued

Table 1. Continued

Study	Agent	Year	Design	Relevant Exclusion Criteria	Results
Prophylaxis of venous thromboembolic disease					
MAGELLAN ¹⁷	Rivaroxaban	2013	Comparison of rivaroxaban (10 mg/d) vs enoxaparin (40 mg once/d) in patients who were hospitalized for an acute medical illness with the outcome of asymptomatic proximal or symptomatic VTE in 10 and 35 d	Conditions that may increase the risk of bleeding, including intracranial hemorrhage, concomitant conditions or diseases that may increase the risk of study subjects or interfere with the study outcome	Rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis. Extended duration rivaroxaban reduced the risk of venous thromboembolism but was associated with an increased risk of major or clinically relevant bleeding
ADOPT ¹⁸	Apixaban	2011	Comparison of apixaban (2.5 mg twice daily for 30 d) vs enoxaparin (40 mg once daily for 6–14 d) in patients who were hospitalized for an acute medical illness with the outcome of VTE or death related to VTE	Patients with VTE, active bleeding or at high risk of bleeding, unable to take oral medication, with diseases requiring ongoing treatment with anticoagulants or antiplatelets other than aspirin at a dose \leq 165 mg/d	Apixaban administration for 30 d did not provide superior thromboprophylaxis compared with enoxaparin for 6–14 d. Apixaban was associated with significantly more major bleeding events than was enoxaparin
APEX ¹⁹	Betrixaban	2016	Comparison of betrixaban (160 mg loading dose and then 80 mg twice daily for 35–42 d) vs enoxaparin 40 mg once daily for 10 \pm 4 d in patients who were hospitalized for acute medical illness and had an elevated D-dimer level with the outcome of VTE	Life expectancy <8 wks. Anticipated need for prolonged anticoagulation during the trial	In patients with acute medical illness and elevated D-dimers, betrixaban was associated with similar rates of VTE and major bleeding with enoxaparin. In patients with acute medical illness and elevated D-dimers or older than 75 y, betrixaban was associated with a 24% risk reduction for VTE, and similar rates of bleeding compared with enoxaparin

AF indicates atrial fibrillation; CrCl, creatinine clearance; DVT, deep venous thrombosis; GI, gastrointestinal; ICH, intracerebral hemorrhage; NOACs, non-vitamin K oral anticoagulants; PE, pulmonary embolism; SSE, stroke or systemic embolism; VKA, vitamin K antagonists; VTE, venous thromboembolic disease.

states, such as the anti-phospholipid syndrome (APS), the nephrotic syndrome, and congenital coagulopathies. Third, the efficacy of NOACs has not been evaluated in patients with advanced renal insufficiency, end-stage renal disease, or hepatic dysfunction. Fourth, important patient subgroups, such as pediatric patients and pregnant women, have not been adequately studied. Last, the prevalence and sequelae of physician underdosing warrants study, as does patient adherence and long-term medication persistence. This review will expand on the treatment gaps in NOAC use and summarize indications where anticoagulation with indirectly acting anticoagulants such as VKAs and heparins will still be considered first-line treatment pending further studies.

Mechanical Prosthetic Valves and Rheumatic Mitral Valve Disease

Valvular heart disease has a prevalence of 2.5% (any valve) in the United States, and is equally distributed between men and

women.²⁷ Prosthetic heart valve replacement is recommended for many patients with severe valvular heart disease²⁸ and on average 300 000 prosthetic heart valve replacements are performed every year worldwide, 100 000 of which are in North America.²⁹ By 2050, the annual number of valve replacements is projected to be 850 000.³⁰ Mechanical valves are more durable than bioprosthetic valves but typically require lifelong anticoagulation therapy.³¹ The use of VKAs provides excellent protection against thromboembolic complications in patients with mechanical heart valves,³¹ but its use is bound by the drawbacks previously described.

Although preclinical studies showed a potential role of NOACs in the presence of a mechanical valve, in the RE-ALIGN trial, dabigatran was associated with increased thromboembolic risk. Patients with severe mitral stenosis or mechanical valves were excluded from the major NOAC trials, and thus their results cannot be generalized in this distinct patient population. In vitro studies have demonstrated that

dabigatran (1 $\mu\text{mol/L}$)³² and high-dose rivaroxaban (300 ng/mL)³³ were as effective as unfractionated heparin and low molecular weight heparin (LMWH) in preventing thrombus formation on mechanical heart valves. In porcine models of heterotopic mechanical valve implantation, dabigatran³⁴ and rivaroxaban³⁵ have been equally effective as enoxaparin in preventing valvular thrombus formation. Dabigatran provides a mortality benefit when compared with warfarin after mechanical mitral valve replacement in pigs.³⁶ However, these results have not been translated in humans. Several case reports demonstrated severe valvular thrombosis when dabigatran was used in the setting of mechanical mitral valve,^{37,38} mechanical aortic valve,³⁹ or rheumatic mitral stenosis.⁴⁰ In the RE-ALIGN phase II clinical trial, patients with mechanical heart valves were randomized to receive either dabigatran (150, 220, or 300 mg twice daily, to achieve serum dabigatran trough concentrations >50 ng/mL) or dose-adjusted warfarin with a target international normalized ratio (INR) of 2 to 3 or 2.5 to 3.5, depending on their thromboembolic risk. The trial was terminated prematurely because of significantly increased thromboembolic and bleeding rates in the dabigatran arm.²⁶ As a result, research for this indication has been stopped, and use of these agents is contraindicated in patients with mechanical prosthetic valves.

There are several potential reasons why dabigatran failed to provide adequate thromboprophylaxis in RE-ALIGN. The dose of dabigatran that was used (trough levels >50 ng/mL) was selected based on studies in AF.¹² The pathophysiology of thrombosis in the setting of mechanical valve implantation is different from that in AF and thus the optimal dabigatran dose in the setting of AF might be higher. In AF, thromboembolic events are thought to occur primarily because of low flow and blood pooling in the left atrium, pro-thrombotic changes in vessel walls, and an imbalance between coagulation and fibrinolysis resulting in a hypercoagulable state.⁴¹ Mechanical valves are associated with abnormal flow and high shearing stress.⁴² A significant release of pro-thrombotic particles and thrombin that occur during cardiopulmonary bypass might predispose patients to thrombotic events.⁴³ Tissue factor released at the site of tissue destruction has been thought to be a major contributor to postoperative thrombosis through activation of the extrinsic coagulation pathway.⁴⁴ In addition, there is activation of the contact coagulation pathway because of the interface of blood with the mechanical valve sewing ring⁴⁵ and valvular disks.⁴⁶ In vitro, dabigatran fails to normalize the increased endogenous thrombin potential of serum exposed to mechanical valves, while warfarin is able to normalize it.⁴⁷ Furthermore, during surgery DNA and RNA are released from destroyed tissues and inorganic polyphosphate residues are released from activated platelets. Extracellular RNA, released from tissue damage, can bind to factors XII and XI, leading to activation of

the contact coagulation pathway.⁴⁸ Inorganic polyphosphate residues, released from activated platelets, directly bind and activate factor XII.⁴⁹ Recent studies suggest that factor XI and the intrinsic coagulation pathway might be central to the mechanism of postoperative thrombosis, since selective inhibition of factor XI with anti-sense oligonucleotides reduces the rates of thrombosis.⁵⁰

In RE-ALIGN, most valvular thrombosis occurred in the immediate postoperative period,²⁶ suggesting that the increased release of pro-thrombotic substances after surgery overwhelms the capacity of dabigatran to antagonize thrombin. Anticoagulation in this setting should occur with frequent and individualized dose adjustments that match the unpredictably released pro-coagulant factors and maintain a net anticoagulant effect.⁵¹ Although by study design dabigatran was dosed up to twice the Food and Drug Administration approved dose for AF, to achieve circulating levels >50 ng/mL, this might not reflect the true anticoagulation effect of dabigatran, at the valve level, in the setting of unpredictable bursts of pro-thrombotic factors after surgery. However, patients receiving dabigatran had a higher risk of bleeding compared with those receiving VKA. Contrary to this, INR measurements reflect the net anticoagulation effect of VKAs and enable individualized dose adjustment to achieve the desired level of anticoagulation. Given their short half-lives, monitoring the net anticoagulation effect of NOACs in this dynamic setting would be challenging. Furthermore, dabigatran is a competitive inhibitor of a single coagulation factor while VKAs are noncompetitive irreversible inhibitors of multiple coagulation factors of both the intrinsic and extrinsic coagulation pathways, as well as of factor X and thrombin in the common pathway.⁵²

VKAs remain the anticoagulation modality of choice in patients with mechanical valves.³¹ In a meta-analysis of 46 anticoagulation studies and 53 647 patients with mechanical valves, a mechanical valve in the mitral position was associated with a 2-fold higher thromboembolic risk compared with the aortic position. Anticoagulation with warfarin was an effective approach for the reduction of thromboembolic events.⁵³ High INR variability is independently associated with reduced survival after a mechanical valve implantation.⁵⁴ There is limited experience on the safety and efficacy of NOACs in patients with AF and biological prosthesis or mitral valve repair.⁵⁵

Regarding patients with rheumatic mitral valve disease, the American College of Chest Physicians guidelines recommend anticoagulation with VKAs in the presence of left atrial enlargement (>55 mm), left atrial thrombus, AF, or history of systemic embolism.³¹ There are no randomized controlled clinical trials assessing the benefit of VKAs in patients with rheumatic valve disease, and these recommendations are primarily based on observational studies.^{56,57} Patients with rheumatic mitral valve disease were excluded from all major

NOAC trials and their use should be avoided until further studies become available.

Cancer-Associated Thrombosis

Venous thromboembolism is an increasingly common complication in patients with cancer. Patients with cancer have on average 4 to 7 times higher risk of developing VTEs compared with noncancer patients, and 20% to 30% of first episodes of VTE are associated with cancer.⁵⁸ The prognosis of cancer patients who develop a VTE is poor, and VTE is the second leading cause of death in these patients.⁵⁹ Management of cancer-associated VTE is particularly challenging as the annual VTE recurrence rate approaches 21% to 27%, which is 2- to 6-fold higher than noncancer patients.^{60,61} In addition, bleeding complications associated with treatment are 2 to 3 times higher than in noncancer patients, with an incidence rate of 12% to 13% per year.^{60,61} The management of cancer-associated thrombosis occurs in 3 different settings: treatment of acute VTE, prevention of VTE in hospitalized medical or surgical patients, and primary prevention of VTE in ambulatory cancer patients receiving chemotherapy.

There are several concerns related to the use of NOACs for VTE prophylaxis or treatment in patients with cancer. First, the exact mechanism of cancer-associated VTE is not entirely understood, but it is likely multifactorial (eg, increased expression of tissue factor, apoptosis, formation of microparticles, and deleterious effects of chemotherapy on vascular endothelium). NOACs target single coagulation factors and may not be able to adequately block the upregulation of the coagulation system that occurs in many types of cancer. A post hoc analysis of the subgroup of cancer patients enrolled in MATISSE-DVT (Mondial Assessment of Thromboembolism Treatment Initiated by Synthetic Pentasaccharide with Symptomatic Endpoints) demonstrated a trend toward higher VTE recurrence rates in the fondaparinux group, an indirect factor Xa inhibitor, compared with the LMWH group.⁶² Second, cancer cells may alter the efficacy of the antithrombotic agents. In an *in vitro* study, the type of cancer cells affected the antithrombotic efficacy of specific factor Xa inhibitors but not the potency of enoxaparin.⁶³ Third, NOACs interfere with the CYP3A4 (rivaroxaban and apixaban) and the P-glycoprotein system (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban), which play an integral role in the metabolism of several chemotherapeutic agents.⁶⁴ Potent inhibitors or inducers of the CYP3A4 and P-glycoprotein systems will cause clinically significant interactions, and co-administration of these drugs with NOACs should be contraindicated.⁶⁵ Fourth, overexpression of P-glycoprotein on the surface of cancer cells has been associated with multidrug resistance, since P-glycoprotein functions as an

efflux pump and its inhibition has been proposed as a therapeutic strategy to overcome resistance to chemotherapy drugs.⁶⁶ It is unknown whether NOACs, through their interference with the P-glycoprotein pathway, affect the efflux-mediated chemotherapy resistance. Fifth, nausea and vomiting are highly prevalent in patients with cancer, reaching 20% to 30% in patients with advanced cancer,⁶⁷ and this might result in inadequate adherence to oral medication administration. Given the short half-life of NOACs,¹⁰ medication nonadherence and missed doses are expected to expose patients to a high risk of VTE. Last, renal dysfunction is highly prevalent in patients with cancer, and many chemotherapy regimens are also nephrotoxic.⁶⁸ NOACs are renally excreted and might accumulate in patients with renal failure. All NOAC studies excluded patients with severe renal insufficiency.

Treatment of Acute Venous Thromboembolism

LMWH is the standard of care for treatment of cancer-associated VTEs.^{4,69,70} LMWH is superior to VKA in reducing recurrent thromboembolic events in patients with cancer-associated acute VTE.^{71,72} A Cochrane meta-analysis of 7 randomized-controlled trials comparing LMWH with VKA in patients with cancer and VTE found that patients treated with LMWH had up to 50% lower VTE recurrence rates with similar bleeding rates. However, there was no statistically significant survival benefit.⁷³ A different meta-analysis of 16 randomized controlled trials comparing LMWH with unfractionated heparin for the treatment of cancer-associated VTE found a 30% reduction in mortality at 3 months of follow-up with LMWH compared with unfractionated heparin.⁷⁴ In the most recent CATCH trial (Tinzaparin versus Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer), treatment for 6 months with the LMWH tinzaparin was not associated with lower mortality, VTE recurrence, or major bleeding compared with warfarin (goal INR: 2.0–3.0).⁷⁵ In a contemporary network meta-analysis of 10 randomized controlled trials and 3242 patients with cancer, which includes the CATCH trial, LMWH was superior to VKA in preventing recurrent VTE (relative risk [RR]=0.60, 95% confidence interval, 0.45–0.79), and LMWH had similar rates of major bleeding with VKA.⁷⁶

There are no randomized clinical trials to date comparing the efficacy and safety of NOACs to LMWH in patients with cancer and VTE. Of completed VTE studies, patients with cancer represent only 2% to 9% of the total participants (Table 1). Hokusai-VTE compared edoxaban with warfarin in patients with VTE and had the highest enrollment of patients with cancer (n=771).²⁵ In prespecified and post hoc subgroup analysis of Hokusai-VTE in patients with cancer, edoxaban failed to meet the noninferiority margin in preventing recurrent VTE.⁷⁷ However, patients with cancer where use

of LMWH was anticipated were excluded from the trial. In a subgroup analysis of 169 participants of AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) with cancer, apixaban had an efficacy and safety profile similar to that of enoxaparin followed by warfarin.⁷⁸ In a pooled analysis of 335 participants of RE-COVER and RE-COVER II (Dabigatran versus warfarin in the treatment of acute venous thromboembolism) with cancer, dabigatran had similar clinical benefits and rates of bleeding compared with warfarin.⁷⁹ Similar results were reported for rivaroxaban in a pooled analysis of 353 participants of EINSTEIN-DVT (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis) and EINSTEIN-PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism) with cancer.⁸⁰ In a meta-analysis of 6 studies and 1132 patients with cancer and VTE, the rate of recurrence of VTE and the rate of major bleeding were similar between patients treated with a NOAC and warfarin.⁸¹ The results of these studies should be interpreted with caution. First, current trials assessing the efficacy of NOACs in VTE were not designed specifically for patients with cancer. Limited life expectancy was an exclusion criterion and thus the sample of patients with cancer that were enrolled likely represents the healthiest individuals. Second, patients with increased risk of bleeding and advanced renal disease, which is highly prevalent in patients with cancer,⁶⁸ were excluded from these studies. Last, current studies compare NOACs with VKA but not LMWH, which is the standard of care for the treatment of cancer-associated VTEs.

There is limited evidence of NOAC use in these patients. In 3 single-center, single-arm, nonrandomized, open-label cohorts of 200 to 400 patients with cancer-associated VTE, treatment with rivaroxaban for 3 to 6 months was associated with VTE recurrence in 3.3% to 4.4%, and major bleeding occurred in 2.2% to 2.5% of the participants.^{82–84} There are currently several ongoing trials evaluating NOACs in the treatment of VTE in patients with cancer (Table 2). Before these trials conclude, LMWH will remain the standard treatment of cancer-associated VTEs.

Prevention of Venous Thromboembolism in the Hospital Setting

Routine pharmacological VTE prophylaxis is recommended in all patients with cancer who are hospitalized for medical or surgical reasons, both by the European Society of Medical Oncology⁶⁹ and the American Society of Clinical Oncology.⁷⁰ There is little evidence on the use of NOACs for the prevention of VTE in patients with cancer who are hospitalized because of acute medical or surgical illness. The MAGELLAN (Venous Thromboembolic Event [VTE] Prophylaxis in Medically Ill

Patients) trial compared rivaroxaban with enoxaparin in patients who were hospitalized for an acute medical illness and demonstrated that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days). Extended duration of rivaroxaban treatment (35 days) reduced the risk of venous thromboembolism but was associated with an increased risk of bleeding.¹⁷ The ADOPT (Study of Apixaban for the Prevention of Thrombosis-related Events in Patients With Acute Medical Illness) trial compared administration of apixaban for 30 days to enoxaparin for 6 to 14 days in patients hospitalized for an acute medical illness and demonstrated that an extended course of apixaban was not superior to a short course of enoxaparin in preventing thrombotic events, while it was associated with a significantly higher rate of major bleeding.¹⁸ The recent APEX (Prevention with Extended Duration Betrixaban) trial demonstrated that extended duration betrixaban (35–42 days) was similar to enoxaparin (for 10±4 days) for prevention of VTE in patients with acute medical illness.¹⁹ None of these trials was specific to cancer patients, and only 7.3% to 10.4% of the total participants had cancer. Both trials demonstrated higher bleeding rates with NOACs compared with enoxaparin, suggesting that these agents might not be safe for VTE prophylaxis in patients with cancer because of the patients' higher risk of bleeding.^{60,61} There are no studies to date assessing the use of NOACs in patients with cancer hospitalized for a surgical condition. Currently, there are few ongoing clinical trials assessing apixaban for VTE prophylaxis in patients with cancer undergoing surgery (Table 2).

Primary Prevention of Venous Thromboembolism in the Ambulatory Setting

Thromboprophylaxis in ambulatory patients with cancer is not routinely recommended but it may be considered in selected high-risk individuals, such as patients with multiple myeloma receiving anti-angiogenic agents and/or dexamethasone.⁷⁰ There is only 1 phase II trial evaluating the role of apixaban in primary VTE prophylaxis in ambulatory patients with cancer. In this trial, 125 patients with advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian, or prostate cancer, cancer of unknown origin, myeloma, or selected lymphomas receiving chemotherapy were randomized to receive placebo or apixaban (2.5, 5, or 10 mg twice daily). The rate of major bleeding in the apixaban group was 2.2% and the authors concluded that apixaban was well tolerated, but future studies are warranted to determine a safe regimen for VTE prophylaxis in ambulatory patients receiving chemotherapy.⁸⁵ There are several ongoing clinical trials assessing apixaban for VTE prophylaxis in ambulatory patients with cancer who undergo chemotherapy (Table 2).

Table 2. PICO Model for Planned and Ongoing Clinical Trials Assessing NOACs in Management of Cancer-Associated VTE

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Clinical Trial Registration	Study Start Date	Estimated Completion Date
Treatment of VTE								
Direct oral anticoagulants (DOACs) vs LMWH+/-warfarin for VTE in cancer: a randomized effectiveness trial (CANVAS Trial)	Randomized, parallel assignment, open label trial	Patients with cancer and VTE (within 30 d of enrollment)	Dabigatran Rivaroxaban Apixaban Edoxaban (details not provided)	LMWH alone or with warfarin	Cumulative VTE recurrence	NCT02744092	April 2016	September 2019
Rivaroxaban in the treatment of VTE in cancer patients—a randomized phase III study	Randomized, parallel assignment, open label trial	Patients with active cancer, newly diagnosed VTE, and good performance status	Rivaroxaban (15 mg twice daily for 21 d, followed by 20 mg once daily over a period of 3 mo)	Enoxaparin (1 mg/kg BW twice daily Tinzaparin 175 IE/kg BW once daily Dalteparin 200 IE/kg BW once daily)	Patient-reported treatment satisfaction Secondary: Rate of symptomatic VTE recurrence	NCT02583191	October 2015	March 2018
Efficacy and safety of oral rivaroxaban for the treatment of venous thromboembolism in patients with active cancer. A pilot study (CASTE-DIVA)	Randomized, single-blind clinical trial	Active solid cancer or myeloma treated with immunomodulatory drugs and symptomatic VTE	Rivaroxaban, (15 mg twice/d for 3 wks followed by 20 mg once daily for 9 wks)	Dalteparin, (200 IU/kg once daily for 4 wks followed by 150 IU/kg once daily for 8 wks)	Symptomatic recurrent VTE or worsening of pulmonary vascular or venous obstruction	NCT02746185	December 2015	May 2017
A phase III, randomized, open label study evaluating the safety of apixaban in subjects with cancer-related venous thromboembolism	Randomized, parallel assignment, open-label study	Active cancer (except nonmelanoma skin cancer), and confirmed acute VTE	Apixaban 10 mg twice daily on d 1–7 and 5 mg apixaban twice daily on d 8–180	Dalteparin (200 IU/kg/d on d 1–30 and 150 IU/kg/d on d 31–180)	Any episode of major bleeding including fatal bleeding	NCT02585713	October 2015	December 2020
Apixaban as treatment of venous thrombosis in patients with cancer: the CAP study	Single-group, open-label, study	Active cancer other than basal-cell or squamous-cell carcinoma of the skin and confirmed VTE	Apixaban (10 mg 2 times daily for 1 wk, then apixaban 5 mg 2 times daily for 6 mo, then apixaban 2.5 mg 2 times daily for as long as the treating physician finds it necessary)	N/A	Recurrent confirmed VTE or VTE-related death Major or clinically relevant nonmajor bleeding	NCT02581176	October 2015	April 2016

Continued

Table 2. Continued

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Clinical Trial Registration	Study Start Date	Estimated Completion Date
Rivaroxaban for the prevention of venous thromboembolism in Asian patients with cancer	Single-arm study	Asian patients with cancer-associated VTE	Rivaroxaban (15 mg twice/d for the first 3 wks, followed by 20 mg once daily)	None	Recurrence of VTE	NCT01989845	October 2013	February 2017
SELECT-D: anticoagulation therapy in SELECTed cancer patients at risk of recurrence of venous thromboembolism	Randomized, open label, multicenter pilot study	Patients with cancer and acute VTE	Rivaroxaban (details not provided)	Dalteparin	Recurrence of VTE	ISRCTN86712308	January 2013	December 2018
Cancer VTE	Randomized controlled, clinical trial	Patients with cancer and acute VTE	Edoxaban (details not provided)	Dalteparin	Recurrence of VTE	NCT02073682	March 2015	December 2017
Prevention of VTE								
Efficacy and safety of rivaroxaban prophylaxis compared with placebo in ambulatory cancer patients initiating systemic cancer therapy and at high risk for venous thromboembolism	Randomized, double-blind, placebo-controlled clinical trial	Patients with active malignancy and good performance status who plan to initiate systemic chemotherapy within ± 1 wk of receiving the first study drug dose	Rivaroxaban (10 mg daily for 180 d)	Placebo	First confirmed VTE or VTE-related death	NCT02555878	September 2015	January 2018
The safety of oral apixaban (Eliquis) vs subcutaneous enoxaparin (Lovenox) for thromboprophylaxis in women with suspected pelvic malignancy: a prospective randomized open blinded end point (PROBE) design	Randomized, single-blind, safety study	Women with pelvic malignancy undergoing surgical debulking	Apixaban (2.5 mg twice daily for 28 d postsurgery)	Enoxaparin (40 mg daily for 28 d postsurgery)	Incidence of major bleeding	NCT02366871	February 2015	March 2018

Continued

Table 2. Continued

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Clinical Trial Registration	Study Start Date	Estimated Completion Date
A phase III randomized, open label, multicenter study of the safety and efficacy of apixaban for thromboembolism prevention vs no systemic anticoagulant prophylaxis during induction chemotherapy in children with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoma (T or B cell) treated with pegylated L-asparaginase	Randomized, open-label, placebo-controlled clinical trial	Children with new diagnosis of de novo acute lymphocytic leukemia or lymphomas and planned induction chemotherapy with a corticosteroid, vincristine, and PEG L-asparaginase, with or without daunorubicin	Apixaban (if <35 kg of 0.07 mg/kg twice a day 25–28 d, if ≥35 kg either 2.5 mg tablet twice a day or 6.2 mL of the 0.4 mg/mL solution twice a day for 25–28 d)	Placebo	Composite of nonfatal VTE and VTE-related death major bleeding	NCT02369653	April 2015	May 2020
Apixaban for the prevention of venous thromboembolism in cancer patients (AVERT)	Randomized controlled, double-blind placebo-controlled clinical trial	Patients with cancer, undergoing surgery	Apixaban (2.5 mg twice/d)	Placebo	First episode of VTE	NCT02048865	January 2014	January 2017
Apixaban for primary prevention of venous thromboembolism in patients with multiple myeloma receiving immunomodulatory therapy	Randomized, double-blind, placebo-controlled clinical trial	Current or prior diagnosis of symptomatic multiple myeloma that will be starting or already receiving immunomodulatory therapy (thalidomide, lenalidomide, or pomalidomide)	Apixaban (2.5 mg orally twice daily for primary prevention of VTE for a duration of 6 mo)	Placebo	Symptomatic VTE Major and clinically relevant nonmajor bleeding	NCT02956969	January 2017	December 2019
Evaluation of the use of apixaban in prevention of thromboembolic disease in patients with myeloma treated with IMiDs (MYELAXAT)	Single-arm study	Patients with myeloma who are treated with melphalan, prednisone, thalidomide, lenalidomide, or dexamethasone	Apixaban (2.5 mg twice/d)	None	VTE and VTE-related death Major and clinically relevant nonmajor bleeding	NCT02066454	April 2014	July 2017

BW indicates body weight; IU, International Unit; LMWH, low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VTE, venous thromboembolic disease.

Until the safety and efficacy of NOACs are compared with LMWH in randomized clinical trials of patients with cancer, conventional treatment with LMWH will remain the standard of care for the management of thromboembolic disease in these patients. Unfortunately, contemporary analysis of practice patterns in the United States and Germany demonstrates that LMWH is underutilized for treatment and prevention of cancer-related VTE, and VKA is the preferred anticoagulant, despite guideline recommendations. More patients remained on oral versus injectable agents, which may be related to self-injection burden and costs.^{86,87}

Antiphospholipid Syndrome

APS is defined by the occurrence of venous and/or arterial thrombosis and/or pregnancy morbidity, in the setting of persistent circulating antiphospholipid antibodies (aPLs).⁸⁸ There are 3 types of aPLs used in the Sydney criteria to diagnose APS: anti-beta2-glycoprotein I, anticardiolipin, and antibodies detected by lupus-anticoagulant assays (anti-beta2-glycoprotein I or antiprothrombin).⁸⁸ Additional antibodies directed against phospholipid/phospholipid-protein have been causally linked to APS (IgA and IgM anticardiolipin, IgA and IgM beta-2 glycoprotein I, anti-phosphatidylserine antibodies, anti-phosphatidylethanolamine antibodies, antiprothrombin antibodies, and antibodies against the phosphatidylserine-prothrombin complex). Presence of aPLs in the serum does not necessarily translate to APS, but it is associated with a broad spectrum of clinical manifestations ranging from asymptomatic seropositivity to thrombotic microangiopathy with multiorgan involvement and failure.⁸⁸ The exact mechanisms of APS remain largely unknown but a “2-hit” model has been proposed where the first hit is the presence of aPLs and the second hit is frequently related to activation of the innate immune system.⁸⁹

The 14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends recommends that VKAs should be the first-line anticoagulation in patients with thrombotic APS.⁹⁰ Although there is some controversy on the therapeutic goals of anticoagulation in patients with APS, evidence suggests that the target INR should be between 2.0 and 3.0, since patients treated to a higher INR goal (3.0–4.0) have the same rate of thrombotic recurrence but higher incidence of bleeding.^{91,92} Management of anticoagulation with VKAs in patients with APS is particularly challenging. In addition to the issues inherent to VKA use, monitoring of anticoagulation may be complicated by the variable responsiveness of thromboplastin reagents to aPLs, which may potentially influence the validity of INR measurement.⁹³

The pathophysiology of thrombosis in APS is complex and incompletely understood. APS is governed by massive release

of thrombin^{94,95} and tissue factor,^{96,97} as well as augmented activation of multiple coagulation factors.^{98,99} NOACs that selectively inhibit 1 coagulation factor might provide inadequate protection in this setting. In a murine model of obstetric APS, hirudin (direct thrombin inhibitor) and fondaparinux (indirect factor Xa inhibitor) were ineffective in preventing pregnancy loss. Both unfractionated heparin and LMWH (indirect inhibitors of multiple factors) prevented miscarriages, suggesting that selective factor inhibition might not be an adequate anticoagulation strategy in APS.¹⁰⁰ However, there is conflicting evidence on the clinical use of anticoagulation for prevention of pregnancy loss in patients with APS, and this discussion is beyond the scope of this review.

There are limited clinical data on the safety and efficacy of NOACs in patients with APS. The rivaroxaban trials (EINSTEIN-DVT and EINSTEIN-PE) included a small subset of patients with known thrombophilic conditions (5–7%) including some patients with aPLs. The sample size of those patients is limited and details on the antibody profile or APS status are not available. The results of these studies cannot be generalized to patients with APS.¹⁰¹ In small case series, dabigatran and rivaroxaban have failed to prevent thrombosis in patients with APS.^{101,102} In RAPS (Rivaroxaban in Anti-Phospholipid Syndrome), patients with APS and a history of VTE who had been on warfarin (INR range between 2.0 and 3.0) for at least 6 months were randomized to receive rivaroxaban 20 mg once daily (or 15 mg once daily if creatinine clearance is 30–49 mL/min, n=116) or continue warfarin with a target INR of 2.5 (n=54). The primary outcome was percentage change in endogenous thrombin potential from randomization to day 42. Rivaroxaban failed to reach the noninferiority threshold in reducing endogenous thrombin potential. There was no increase in thrombotic risk in patients treated with rivaroxaban compared with standard-intensity warfarin, although this small study was not powered for efficacy.¹⁰³ There are 3 ongoing clinical trials currently evaluating NOACs in patients with APS. TRAPS (Trial on Rivaroxaban in AntiPhospholipid Syndrome, NCT02157272) is a multicenter, randomized, open-label study that evaluates whether rivaroxaban 20 mg once daily (or 15 mg in patients with moderate renal insufficiency) is noninferior to warfarin (INR target 2.5), for the prevention of thromboembolic events, major bleeding, and death in high-risk patients with antiphospholipid syndrome.¹⁰⁴ Rivaroxaban for Patients With Antiphospholipid Syndrome (NCT02926170) is a randomized open-label clinical trial comparing the efficacy and safety of rivaroxaban (20 mg daily) with dose-adjusted acenocoumarol in patients with thrombotic antiphospholipid syndrome who are treated with VKA for at least 6 months. ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis among Patients with Antiphospholipid Syndrome, NCT02295475) is a prospective, randomized, open-label, blinded event pilot study. In this study, patients with antiphospholipid syndrome who have been on

anticoagulation for secondary prevention of thrombosis are randomized to receive apixaban 5 mg twice a day or adjusted-dose warfarin and the safety and efficacy of the 2 strategies will be compared.¹⁰⁵ Until the results of these trials provide evidence of efficacy and safety of NOACs in patients with APS, according to the task force report on antiphospholipid syndrome treatment trends, NOACs should be considered in APS patients with VTE only when there is known VKA allergy, intolerance, or poor anticoagulant control.⁹⁰

Other Hypercoagulable States

Very limited data exist on the role of NOACs in other hypercoagulable states such as inherited coagulopathies (homozygous factor V Leiden mutation, protein C or S deficiency, elevated levels of factors VII–XII), or the nephrotic syndrome. Individuals with these conditions were significantly underrepresented in the current trials. Dabigatran was prescribed in a 21-year-old woman with recurrent VTEs caused by protein C deficiency, complicated by warfarin-induced skin necrosis, and inability to maintain anticoagulation on LMWH. The patient did not experience any VTE recurrence in 6 months of follow-up.¹⁰⁶ Rivaroxaban was prescribed to a 30-year-old woman who had homozygosity of factor V Leiden mutation and who sustained an ovarian vein thrombosis with proximal extension to the renal vein. The patient remained free of symptoms without recurrence of thrombi or bleeding complications.¹⁰⁷ Dabigatran¹⁰⁸ and rivaroxaban¹⁰⁹ have been used for secondary prophylaxis in a few patients with nephrotic syndrome. Anticoagulation in these patients has been traditionally achieved with VKAs or heparins.^{110,111}

Other Considerations

End-Stage Renal Disease

Currently available NOACs are primarily renally excreted. Dabigatran is 80% renally excreted, while the renal excretion of factor Xa inhibitors ranges between 6% and 13% (betrixaban) and 50% (edoxaban).¹¹² Clinical trials included patients with mild to moderate renal disease with assigned lower study dose in most of these trials. Rivaroxaban 15 mg once per day^{13,15} and edoxaban 30 mg once per day¹⁶ were used in patients with creatinine clearance between 30 and 49 mL/min. The dose of apixaban was reduced to 2.5 mg twice daily in the presence of 2 of 3 factors (age >80 years, weight <60 kg, creatinine 1.5 mg/dL or greater). The proportion of patients with moderate renal disease (creatinine clearance of 30–49 mL/min) that enrolled in these trials ranged between 15% and 21%. In a study of 14 264 patients with nonvalvular AF and creatinine clearance of 30 to 49 mL/min, rivaroxaban

15 mg per day had similar efficacy and safety compared with dose-adjusted warfarin.¹¹³ A meta-analysis of 10 trials and 40 693 patients with creatinine clearance of 30 to 49 mL/min suggested that NOACs are noninferior to standard anticoagulation, and they are associated with less bleeding.¹¹⁴ However, clinical trials excluded patients with severe renal insufficiency (creatinine clearance <30 mL/min for dabigatran, rivaroxaban, and edoxaban and <25 mL/min for apixaban) and those on dialysis. There are limited data on the efficacy and safety of NOACs in these patient populations. Despite the dearth of data, there is a reported increase in the number of NOAC prescriptions in patients on dialysis.¹¹⁵ In pharmacokinetic and pharmacodynamic simulation studies, most NOAC administration in patients on dialysis could potentially result in higher levels compared with those without renal impairment.^{116–118} In a small pharmacokinetic, pharmacodynamic, and safety study, patients with end-stage renal disease on dialysis (n=8) had a modest increase (36%) in apixaban area under the curve and no increase in apixaban maximal concentration compared with subjects with normal renal function (n=8). Hemodialysis had a limited impact on apixaban clearance.¹¹⁹ These data resulted in the Food and Drug Administration revising the label of apixaban and recommending that 5 mg twice daily can be used in patients with end-stage renal disease on hemodialysis, while 2.5 mg twice daily should be used in patients who are older than 80 years of age or weigh <60 kg. Until clinical data on the safety and efficacy of other NOACs in patients with end-stage renal disease or on dialysis become available, apixaban could be used with caution while other NOACs should not be used in these patients. VKAs have been the standard anticoagulation treatment, although a clear benefit over risk has not been demonstrated, and more data are needed for this challenging group of patients.¹²⁰

Another area of uncertainty is the use of NOACs in patients whose renal function fluctuates widely over time or who are at heightened risk for acute kidney injury, such as patients with advanced heart failure. Patients with AF and a $\geq 25\%$ relative decrease in their estimated glomerular filtration rate had a 2-fold higher risk of ischemic stroke.¹²¹ Acute and chronic renal dysfunction is common among individuals requiring long-term anticoagulant therapy.¹²² Patients with impaired renal function represent a distinct high-risk group and there are limited data on what the optimal strategy of anticoagulation should be.

Pediatric Patients

The efficacy and safety of NOACs in pediatric patients is not established. Pediatric VTE is uncommon; however, its incidence has been increasing over the past 2 decades.¹²³ Heparin and VKAs have been traditionally used in this

population, mostly by extrapolation of results of studies in adults. The hemostatic system undergoes significant changes in neonatal life and, especially during the first year of life, levels of pro- and anticoagulant factors are low compared with adults.¹²⁴ For this reason, the net anticoagulant effect of selective factor inhibition with NOACs in neonates and children might be different from adults. There are limited data on the safety and efficacy of NOACs in neonates and children. In *in vitro* studies of plasma spiked with dabigatran¹²⁵ and rivaroxaban,¹²⁶ the changes in hemostatic parameters were similar in children and adults. However, clotting time was longer in neonatal plasma spiked with dabigatran¹²⁷ and rivaroxaban¹²⁸ compared with adult serum, suggesting that neonatal plasma may be more sensitive to those agents compared with adults. There is only 1 phase II clinical trial available evaluating dabigatran in adolescents. In this trial (n=9, age: 12–18 years old), dabigatran doses of initially 1.71 ($\pm 10\%$) mg/kg for 3 days, followed by 2.14 ($\pm 10\%$) mg/kg (target adult dose adjusted for patient's weight) was well tolerated over the 3-day treatment period, with the exception of occurrence of dyspepsia in 2 patients. The observed dabigatran pharmacokinetics and pharmacodynamics were similar to that of adults.¹²⁹ There are no available studies assessing the efficacy and safety of apixaban and edoxaban in pediatric patients. However, there are several ongoing clinical trials evaluating the safety and efficacy of NOACs in pediatric patients (Table 3). Until the results of these studies are available, heparin and VKA should remain the standard of care in pediatric patients.

Pregnancy

There are very limited data on the safety of NOAC use during pregnancy.¹³⁰ All major NOAC trials excluded patients who were pregnant. In *ex vivo* studies of perfused placentas, unbound dabigatran,¹³¹ unbound rivaroxaban,¹³² and unbound apixaban¹³³ can cross the placenta with transfer ratios of 33%, 69%, and 77%, respectively. Apixaban levels in cord blood are predicted to be 35% to 90% of the corresponding maternal levels.¹³³ This evidence suggests that NOACs can reach the fetus and potentially have adverse effects on fetal and neonatal coagulation. Dabigatran, rivaroxaban, and edoxaban are classified by the Food and Drug Administration as a pregnancy class C: "risk cannot be ruled out." Apixaban is classified as a pregnancy class B: "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women." Betrixaban was not associated with adverse developmental fetal outcomes, but maternal hemorrhage was observed, in preclinical animal studies.¹³⁴ There are no clinical trials of NOACs in pregnancy. In an

analysis of 137 cases of women who were exposed to NOACs during pregnancy, fetal abnormalities were present in 7 (5.1%) patients of which 3 (2.2%) could potentially be interpreted as embryopathy.¹³⁵ In a pharmacovigilance case-series from Germany, 37 pregnancies were prospectively ascertained and resulted in 6 spontaneous abortions, 8 elective terminations of pregnancy, and 23 live births. There was 1 major malformation (conotruncal cardiac defect) in a woman with a previous fetus with cardiac malformation without exposure to rivaroxaban. All women had discontinued rivaroxaban after recognition of pregnancy, mostly in the first trimester, but in 1 woman treatment continued until gestational week 26.¹³⁶ LMWH does not cross the placenta, is efficacious during pregnancy, and is currently the recommended anticoagulant during pregnancy.¹³⁷ Until evidence on the safety of NOACs in pregnancy is available, LMWH should be the anticoagulant of choice in pregnancy. It is uncertain whether NOACs are excreted in breast milk and thus all NOACs should be avoided during lactation.

Drug Adherence and Physician Underdosing

The effect of medication adherence among patients prescribed NOACs has not been adequately assessed to date. Medication nonadherence is a very common and perplexing issue. Approximately 50% of patients fail to comply with their prescribed medication regimen, independently of sex, age, and medical condition.¹³⁸ Most NOACs have a short half-life, ranging from 6 to 8 (apixaban and edoxaban) to 12 to 17 hours (dabigatran and rivaroxaban).¹¹² The half-life of betrixaban is 37 hours. Warfarin has an average half-life of 40 to 60 hours. For this reason, medication nonadherence will be less tolerated with NOACs as compared with warfarin. In a small cohort of 347 patients studied over a year, 36% of out-of-range INRs were caused by nonadherence.¹³⁹ Warfarin nonadherence is associated with increased health-related costs.¹⁴⁰ In a recent real-world analysis of >36 000 patients with nonvalvular AF, there was a concerning low adherence to NOAC therapy with proportion of days covered ranging between 69.2% and 80% over 6 months of follow-up.^{141,142} The cost of treatment is directly associated with medication nonadherence.¹⁴³ NOACs are significantly more expensive compared with VKAs; the annual cost for NOACs is estimated to be around \$3000 to \$3500, compared with warfarin, which is around \$50.¹⁴⁴ In clinical trials, given the strict protocols and close follow-up, medication nonadherence is infrequently an issue, but adherence outside of this structured setting can be problematic.

Last, there is emerging evidence of a concerning prevalence of NOAC underdosing in routine clinical practice. One out of 8 patients participating in the ORBIT-II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)

Table 3. PICO Model for Planned and Ongoing Clinical Trials Assessing NOACs in Pediatric Patients

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Clinical Trial Registration	Study Start Date	Estimated Completion Date
Open label study comparing efficacy and safety of dabigatran etexilate to standard of care in pediatric patients with venous thromboembolism (VTE)	Open-label, randomized, parallel-group clinical trial	Children <18 y old with VTE	Age and weight appropriate dabigatran twice/d dosing	VKA or LMWH	Combined: complete thrombus resolution, recurrent VTE, and mortality related to VTE	NCT01895777	September 2013	June 2018
Safety of dabigatran etexilate in blood clot prevention in children	Open-label, single-arm prospective cohort study	Children <18 y old with history of VTE and at least 1 risk factor for continuation of anticoagulation therapy	Age and weight appropriate dabigatran twice/ d dosing	None	Recurrence of VTE at 6 and 12 mo, major and minor bleeding	NCT02197416	September 2014	November 2018
EINSTEIN Junior Phase II: oral rivaroxaban in young children with venous thrombosis	Open-label, single-arm study	Children 6 mo to <6 y old who have been treated for at least 2 mo with LMWH and/or VKA for VTE	Age and weight appropriate rivaroxaban once per day dosing	None	Incidence of major bleeding and clinically relevant nonmajor bleeding	NCT02309411	January 2015	April 2017 (results pending)
Rivaroxaban for treatment in venous or arterial thrombosis in neonates	Open-label, single-arm study	Neonates and infants <6 mo who have been treated for at least 5 d with heparin and/or VKA for arterial or venous thrombosis	Weight-adjusted rivaroxaban oral suspension (0.1%) for 7 d	None	Plasma concentration of rivaroxaban, anti-Xa activity	NCT02564718	November 2015	December 2017
EINSTEIN Junior Phase III: oral rivaroxaban in children with venous thrombosis	Multicenter, open-label, active-controlled, randomized clinical trial	Children aged 6 mo to 18 y old with confirmed VTE who receive initial treatment with heparin and require anticoagulation for at least 90 d	Age- and weight-appropriate rivaroxaban once per day dosing	LMWH or VKA	Symptomatic recurrent venous thromboembolism, major and clinically relevant nonmajor bleeding	NCT02234843	November 2014	July 2019
Phase I study on rivaroxaban granules for oral suspension formulation in children	Open-label, single-arm pharmacokinetics study	Children 2 mo to 12 y old with previous VTE	Rivaroxaban granules for oral suspension	None	Area under the curve and maximum observed drug concentration	NCT02497716	November 2015	December 2017
Study to evaluate a single dose of apixaban in pediatric subjects at risk for a thrombotic disorder	Open-label, single-arm study	Neonates to <18 y old and any stable disease that are at risk for venous or arterial thrombus	Apixaban solution	None	Area under the curve, maximum observed drug concentration, and estimated time at which maximum plasma concentration occurs	NCT01707394	January 2013	October 2017

Continued

Table 3. Continued

Trial	Design	Patient Population	Intervention	Comparison	Primary Outcome	Clinical Trial Registration	Study Start Date	Estimated Completion Date
A study of the safety and effectiveness of apixaban in preventing blood clots in children with leukemia who have a central venous catheter and are treated with pegylated (PEG) L-asparaginase	Randomized, open label, multicenter clinical trial	Children 1–18 y old with new diagnosis of acute leukemias or lymphomas and planned induction chemotherapy with corticosteroid, vincristine, and PEG L-asparaginase	Weight-adjusted apixaban solution for 25– 28 d	Placebo	Composite of nonfatal VTE and VTE-related death, major bleeding	NCT02369653	April 2015	May 2020
Apixaban for the acute treatment of venous thromboembolism in children	Randomized, open-label, active controlled clinical trial	Children 12– 18 y old who present with VTE and requiring anticoagulation for >12 wks	Age and weight appropriate apixaban twice per day dosing	Standard of care anticoagulation according to local practices	Composite of any VTE and VTE-related mortality, major and clinically relevant nonmajor bleeding	NCT02464969	November 2015	October 2020
Phase 1 pediatric pharmacokinetics/ pharmacodynamics (PK/PD) study	Open-label, single-dose, nonrandomized study	Children <18 y old who continue to require anticoagulation therapy and will abstain from the use of nonsteroidal anti-inflammatory medications	Age and weight appropriate edoxaban once per day dosing	None	Pharmacokinetics and pharmacodynamics parameters of edoxaban	NCT02303431	August 2014	December 2017
Hokusai study in pediatric patients with confirmed VTE	Open-label, randomized, multicenter, controlled clinical trial	Children <18 y old with VTE requiring anticoagulation for >90 d who have received at least 5 d of heparin	Age- and weight-appropriate edoxaban once per day dosing	VKA or heparin	Composite of symptomatic and recurrent VTE, VTE-related death and no change or extension of thrombotic burden	NCT02303431	April 2017	December 2021

LMWH indicates low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists; VTE, venous thrombotic disease.

registry (5738 patients, 242 community sites) was taking a NOAC dose inconsistent with labeling.¹⁴⁵ Older age, female sex, higher CHA₂DS₂-VASc score, and higher bleeding risk were associated with higher risk for underdosing. NOAC underdosing is associated with a 26% increase in cardiovascular hospitalizations. In a large, international, prospective registry from Europe, 15% of patients with creatinine clearance \geq 50 mL/min inappropriately received the lower rivaroxaban dose of 15 mg daily.¹⁴⁶ In the nationwide RAMSES study (Real-life Multicenter Survey Evaluating Stroke Prevention Strategies in Turkey), off-label use of NOACs occurred in 40.2% of the patients, with 30.4% being underdosed.¹⁴⁷ Single-center reports from around the world reveal rates of underdosing as high as 48% to 71% (Australia¹⁴⁸) and 12.4% to 36.9% (United States^{148,149}). Data from clinical practice need to be analyzed to better understand the efficacy and safety of NOACs in the setting of medication nonadherence and off-label use of lower doses.

Conclusions and Future Directions

The non-vitamin K oral anticoagulants constitute a major breakthrough in the management of thromboembolic disease. The ease of their use, the wide therapeutic window, and the fact that they do not require monitoring will help to overcome the significant obstacles encountered with VKAs. The studies conducted to date justify their use in patients with nonvalvular AF, and for VTE prophylaxis and treatment. However, there are specific conditions, such as valvular heart disease, cancer-associated VTE, APS, and other hypercoagulable states, severe renal and hepatic dysfunction, pediatric patients, and pregnancy, where the efficacy and safety of NOACs have yet to be demonstrated. From a translational science perspective, it is essential to elucidate the mechanisms of thrombosis in these conditions. Determining the factors that have a nodal role in these diseases would lay the theoretical ground for developing anticoagulation strategies, specific for each disease, that achieve the maximal antithrombotic effect while minimizing hemorrhagic complications. From a clinical perspective, given the complexity and the challenges inherent to the management of these diseases, well-designed randomized clinical trials should be performed specifically in patients with these medical conditions. Until such data become available, traditional anticoagulation with VKAs or heparins will remain the mainstay of anticoagulation therapy.

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