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

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Vitamin K antagonists (VKAs) were first introduced in the 1920s from studies on the "hemorrhagic" effect of spoiled sweet clover consumption by cattle[1] 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 VTE[4] 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 Etexilate 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

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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)

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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 venus 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 ≤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±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 disease[28] 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 μmol/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, dabigatran[34] and rivaroxaban[35] 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 ring[45] 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 coadministration 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 Oncology[69] 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

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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

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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	NCT02958969	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.

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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, anti-prothrombin 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] Dabigatran[108] and rivaroxaban[109] 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 day[16] 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 ≥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 dabigatran[125] and rivaroxaban,[126] the changes in hemostatic parameters were similar in children and adults. However, clotting time was longer in neonatal plasma spiked with dabigatran[127] and rivaroxaban[128] 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 (±10%) mg/kg for 3 days, followed by 2.14 (±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 apixaban[133] 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 concerningly 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

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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 thrombolic disease.

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registry (5738 patients, 242 community sites) was taking a NOAC dose inconsistent with labeling.[145] Older age, female sex, higher CHA_2DS_2-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 ≥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% (Australia[148]) 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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References

1. Schofield FW. Damaged sweet clover; the cause of a new disease in cattle simulating haemorrhagic septicemia and blackleg. *J Am Vet Med Assoc*. 1924;64:553–556.
2. Verstraete M, Prentice CR, Samama M, Verhaeghe R. A European view on the North American fifth consensus on antithrombotic therapy. *Chest*. 2000;117:1755–1770.
3. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:160S–198S.
4. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352.
5. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. *Heart*. 2008;94:1607–1613.
6. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA*. 2002;287:1690–1698.
7. Limdi NA, Wadelius M, Cavallari L, Eriksson N, Crawford DC, Lee MT, Chen CH, Motsinger-Reif A, Sagreiya H, Liu N, Wu AH, Gage BF, Jorgensen A, Pirmohamed M, Shin JG, Suarez-Kurtz G, Kimmel SE, Johnson JA, Klein TE, Wagner MJ; International Warfarin Pharmacogenetics C. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood*. 2010;115:3827–3834.
8. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J Thromb Thrombolysis*. 2011;31:326–343.
9. Ezekowitz MD, James KE, Radford MJ, Rickles FR, Redmond N. Initiating and maintaining patients on warfarin anticoagulation: the importance of monitoring. *J Cardiovasc Pharmacol Ther*. 1999;4:3–8.
10. DeWald TA, Becker RC. The pharmacology of novel oral anticoagulants. *J Thromb Thrombolysis*. 2014;37:217–233.
11. Chan NC, Bhagirath V, Eikelboom JW. Profile of betrixaban and its potential in the prevention and treatment of venous thromboembolism. *Vasc Health Risk Manag*. 2015;11:343–351.
12. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; Committee R-LS and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
13. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
14. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; Committee AS and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817.
15. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo

AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; Committees A and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.

16. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
17. Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, Tapson V; Investigators M. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513–523.
18. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI; Investigators AT. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167–2177.
19. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM; Investigators A. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534–544.
20. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; Group R-CS. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352.
21. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; Investigators R-MT and Investigators R-ST. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718.
22. Investigators E, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.
23. Investigators E-P, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.
24. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
25. Hokusai VTEI, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.
26. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214.
27. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292.
28. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:2440–2492.
29. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
30. Yacoub MH, Takkenberg JJ. Will heart valve tissue engineering change the world? *Nat Clin Pract Cardiovasc Med*. 2005;2:60–61.
31. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e576S–e600S.
32. Maegdefessel L, Linde T, Krapiec F, Hamilton K, Steinseifer U, van Ryn J, Raaz U, Buerke M, Werdan K, Schlitt A. In vitro comparison of dabigatran, unfractionated heparin, and low-molecular-weight heparin in preventing thrombus formation on mechanical heart valves. *Thromb Res*. 2010;126:e196–e200.
33. Kaeberich A, Reindl I, Raaz U, Maegdefessel L, Vogt A, Linde T, Steinseifer U, Perzborn E, Hauroeder B, Buerke M, Werdan K, Schlitt A. Comparison of unfractionated heparin, low-molecular-weight heparin, low-dose and high-dose rivaroxaban in preventing thrombus formation on mechanical heart valves: results of an in vitro study. *J Thromb Thrombolysis*. 2011;32:417–425.
34. McKellar SH, Abel S, Camp CL, Suri RM, Ereth MH, Schaff HV. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg*. 2011;141:1410–1416.
35. Greiten LE, McKellar SH, Rysavy J, Schaff HV. Effectiveness of rivaroxaban for thromboprophylaxis of prosthetic heart valves in a porcine heterotopic valve model. *Eur J Cardiothorac Surg*. 2014;45:914–919.
36. Schomburg JL, Medina EM, Lahti MT, Bianco RW. Dabigatran versus warfarin after mechanical mitral valve replacement in the swine model. *J Invest Surg*. 2012;25:150–155.
37. Atar S, Wishniak A, Shturman A, Shtiwi S, Brezins M. Fatal association of mechanical valve thrombosis with dabigatran: a report of two cases. *Chest*. 2013;144:327–328.
38. Kuwauchi S, Watanabe S, Abe K, Yamasaki M, Ito J, Kawazoe K. Thromboembolism in a patient with a mechanical mitral valve during anticoagulation with dabigatran etexilate. *Ann Thorac Surg*. 2013;96:1863–1864.
39. Stewart RA, Astell H, Young L, White HD. Thrombosis on a mechanical aortic valve whilst anti-coagulated with dabigatran. *Heart Lung Circ*. 2012;21:53–55.
40. Luis SA, Poon K, Luis C, Shukla A, Bett N, Hamilton-Craig C. Massive left atrial thrombus in a patient with rheumatic mitral stenosis and atrial fibrillation while anticoagulated with dabigatran. *Circ Cardiovasc Imaging*. 2013;6:491–492.
41. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373:155–166.
42. Ellis JT, Wick TM, Yoganathan AP. Prosthesis-induced hemolysis: mechanisms and quantification of shear stress. *J Heart Valve Dis*. 1998;7:376–386.
43. Nieuwland R, Berckmans RJ, Rotteveel-Eijkman RC, Maquelin KN, Roozendaal KJ, Jansen PG, ten Have K, Eijsman L, Hack CE, Sturk A. Cell-derived microparticles generated in patients during cardiopulmonary bypass are highly procoagulant. *Circulation*. 1997;96:3534–3541.
44. Mackman N. Triggers, targets and treatments for thrombosis. *Nature*. 2008;451:914–918.
45. Dewanjee MK, Gross DR, Zhai P, Lanzo S, Shim H, Park K, Schaeffer DJ, Twardock AR. Thrombogenicity of polyethylene oxide-bonded Dacron sewing ring in a mechanical heart valve. *J Heart Valve Dis*. 1999;8:324–330.
46. Meuris B, Verbeken E, Flameng W. Mechanical valve thrombosis in a chronic animal model: differences between monoleaflet and bileaflet valves. *J Heart Valve Dis*. 2005;14:96–104.
47. Jaffer IH, Stafford AR, Fredenburgh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. *J Am Heart Assoc*. 2015;4:e002322. DOI: 10.1161/JAHA.115.002322.
48. Kannemeier C, Shibamiya A, Nakazawa F, Trusheim H, Ruppert C, Markart P, Song Y, Tzima E, Kennerknecht E, Niepmann M, von Bruehl ML, Sedding D, Massberg S, Gunther A, Engelmann B, Preissner KT. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci USA*. 2007;104:6388–6393.
49. Muller F, Mutch NJ, Schenk WA, Smith SA, Esterl L, Spronk HM, Schmidbauer S, Gahl WA, Morrissey JH, Renne T. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. *Cell*. 2009;139:1143–1156.
50. Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI; Investigators F-AT. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372:232–240.
51. Hylek EM. Dabigatran and mechanical heart valves—not as easy as we hoped. *N Engl J Med*. 2013;369:1264–1266.
52. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e44S–e88S.

53. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89:635–641.

54. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. *J Thorac Cardiovasc Surg*. 2002;123:715–723.

55. Acanfora D, Acanfora C, Scicchitano P, Longobardi M, Furgi G, Casucci G, Lanzillo B, Dentamaro I, Zito A, Incalzi RA, Ciccone MM. Safety and feasibility of treatment with rivaroxaban for non-canonical indications: a case series analysis. *Clin Drug Investig*. 2016;36:857–862.

56. Adams GF, Merrett JD, Hutchinson WM, Pollock AM. Cerebral embolism and mitral stenosis: survival with and without anticoagulants. *J Neurol Neurosurg Psychiatry*. 1974;37:378–383.

57. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *BMJ*. 1964;1:1209–1212.

58. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122:1712–1723.

59. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5:632–634.

60. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100:3484–3488.

61. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol*. 2000;18:3078–3083.

62. van Doormaal FF, Raskob GE, Davidson BL, Decousus H, Gallus A, Lensing AW, Piovella F, Prins MH, Buller HR. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. *Thromb Haemost*. 2009;101:762–769.

63. Rousseau A, Van Dreden P, Mbemba E, Elalamy I, Larsen A, Gerotziafas GT. Cancer cells BXPC3 and MCF7 differentially reverse the inhibition of thrombin generation by apixaban, fondaparinux and enoxaparin. *Thromb Res*. 2015;136:1273–1279.

64. Lee AY, Peterson EA. Treatment of cancer-associated thrombosis. *Blood*. 2013;122:2310–2317.

65. Lee AY, Carrier M. Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants. *Thromb Res*. 2014;133(suppl 2): S167–S171.

66. Binkhathlan Z, Lavasanifar A. P-glycoprotein inhibition as a therapeutic approach for overcoming multidrug resistance in cancer: current status and future perspectives. *Curr Cancer Drug Targets*. 2013;13:326–346.

67. Gordon P, LeGrand SB, Walsh D. Nausea and vomiting in advanced cancer. *Eur J Pharmacol*. 2014;722:187–191.

68. Janus N, Launay-Vacher V, Byloos E, Machiels JP, Duck L, Kerger J, Wynendaele W, Canon JL, Lybaert W, Nortier J, Deray G, Wildiers H. Cancer and renal insufficiency results of the BIRMA study. *Br J Cancer*. 2010;103:1815–1821.

69. Mandala M, Falanga A, Roila F; Group EGW. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011;22(suppl 6):vi85–vi92.

70. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Prestrud AA, Falanga A; American Society of Clinical Oncology Clinical P. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31:2189–2204.

71. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer I. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349:146–153.

72. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, Wong T, Cook R, Solymoss S, Poon MC, Raskob G; Investigators LT. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006;119:1062–1072.

73. Akl EA, Kahale L, Barba M, Neumann I, Labedi N, Terrenato I, Sperati F, Muti P, Schunemann H. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev*. 2014;7:CD006650.

74. Akl EA, Vasireddi SR, Gunukula S, Barba M, Sperati F, Terrenato I, Muti P, Schunemann H. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev*. 2011: CD006649.

75. Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; Investigators C. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015;314:677–686.

76. Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. *Thromb Res*. 2015;136:582–589.

77. Raskob GE, van Es N, Segers A, Angchaisuksiri P, Oh D, Boda Z, Lyons RM, Meijer K, Gudz I, Weitz JI, Zhang G, Lanz H, Mercuri MF, Buller HR; Hokusai VTEi. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol*. 2016;3:e379–e387.

78. Agnelli G, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, Raskob GE, Weitz JI, Yamabe T. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost*. 2015;13:2187–2191.

79. Schulman S, Goldhaber SZ, Kearon C, Kakkar AK, Schellong S, Eriksson H, Hantel S, Feuring M, Kreuzer J. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost*. 2015;114:150–157.

80. Prins MH, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, Davidson BL, Beyer-Westendorf J, Pap AF, Berkowitz SD, Cohen AT, Kovacs MJ, Wells PS, Prandoni P. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol*. 2014;1:e37–e46.

81. Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest*. 2015;147:475–483.

82. Mantha S, Laube E, Miao Y, Sarasohn DM, Parameswaran R, Stefanik S, Brar G, Samedy P, Wills J, Harnicar S, Soff GA. Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. *J Thromb Thrombolysis*. 2017;43:166–171.

83. Wells PS, Theberge IA, Bowdridge JC, Forgie MA, Carrier M. PO-41—rivaroxaban is effective therapy for high risk cancer patients with venous thromboembolic disease. *Thromb Res*. 2016;140(suppl 1):S191–S192.

84. Bott-Kitslaar DM, Saadiq RA, McBane RD, Loprinzi CL, Ashrani AA, Ransone TR, Wolfgram AA, Berentsen MM, Wysokinski WE. Efficacy and safety of rivaroxaban in patients with venous thromboembolism and active malignancy: a single-center registry. *Am J Med*. 2016;129:615–619.

85. Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, Ramirez L, Julian J. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *J Thromb Haemost*. 2012;10:807–814.

86. Khorana AA, Yannicelli D, McCrae KR, Milentijevic D, Crivera C, Nelson WW, Schein JR. Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? *Thromb Res*. 2016;145:51–53.

87. Matzdorff A, Ledig B, Stuecker M, Riess H. Practice patterns for prophylaxis and treatment of venous thromboembolism in German cancer patients. *Oncol Res Treat*. 2016;39:194–201.

88. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295–306.

89. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol*. 2011;7:330–339.

90. Erkan D, Aguiar CL, Andrade D, Cohen H, Cuadrado MJ, Danowski A, Levy RA, Ortel TL, Rahman A, Salmon JE, Tektonidou MG, Willis R, Lockshin MD. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev*. 2014;13:685–696.

91. Crowther M, Crowther MA. Intensity of warfarin coagulation in the antiphospholipid syndrome. *Curr Rheumatol Rep*. 2010;12:64–69.

92. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3:848–853.

93. Crowl A, Schullo-Feulner A, Moon JY. Warfarin monitoring in antiphospholipid syndrome and lupus anticoagulant. *Ann Pharmacother*. 2014;48:1479–1483.
94. Lean SY, Ellery P, Ivey L, Thom J, Oostryck R, Leahy M, Baker R, Adams M. The effects of tissue factor pathway inhibitor and anti-beta-2-glycoprotein-I IgG on thrombin generation. *Haematologica*. 2006;91:1360–1366.
95. Shi T, Iverson GM, Qi JC, Cockerill KA, Linnik MD, Konecny P, Krilis SA. Beta 2-glycoprotein I binds factor XI and inhibits its activation by thrombin and factor XIIa: loss of inhibition by clipped beta 2-glycoprotein I. *Proc Natl Acad Sci USA*. 2004;101:3939–3944.
96. Motoki Y, Nojima J, Yanagihara M, Tsuneoka H, Matsui T, Yamamoto M, Ichihara K. Anti-phospholipid antibodies contribute to arteriosclerosis in patients with systemic lupus erythematosus through induction of tissue factor expression and cytokine production from peripheral blood mononuclear cells. *Thromb Res*. 2012;130:667–673.
97. Nojima J, Masuda Y, Iwatani Y, Suehisa E, Futsukaichi Y, Kuratsune H, Watanabe Y, Takano T, Hidaka Y, Kanakura Y. Tissue factor expression on monocytes induced by anti-phospholipid antibodies as a strong risk factor for thromboembolic complications in SLE patients. *Biochem Biophys Res Commun*. 2008;365:195–200.
98. Giannakopoulos B, Gao L, Qi M, Wong JW, Yu DM, Vlachoyiannopoulos PG, Moutsopoulos HM, Atsumi T, Koike T, Hogg P, Qi JC, Krilis SA. Factor XI is a substrate for oxidoreductases: enhanced activation of reduced FXI and its role in antiphospholipid syndrome thrombosis. *J Autoimmun*. 2012;39:121–129.
99. Galli M, Willems GM, Rosing J, Janssen RM, Govers-Riemslag JW, Comfurius P, Barbui T, Zwaal RF, Bevers EM. Anti-prothrombin IgG from patients with anti-phospholipid antibodies inhibits the inactivation of factor Va by activated protein C. *Br J Haematol*. 2005;129:240–247.
100. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nat Med*. 2004;10:1222–1226.
101. Schaefer JK, McBane RD, Black DF, Williams LN, Moder KG, Wysokinski WE. Failure of dabigatran and rivaroxaban to prevent thromboembolism in antiphospholipid syndrome: a case series of three patients. *Thromb Haemost*. 2014;112:947–950.
102. Signorelli F, Nogueira F, Domingues V, Mariz HA, Levy RA. Thrombotic events in patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight cases. *Clin Rheumatol*. 2016;35:801–805.
103. Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, Sylvestre Y, Machin SJ, Bertolaccini ML, Ruiz-Castellano M, Muirhead N, Dore CJ, Khamashta M, Isenberg DA; Investigators Rt. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol*. 2016;3:e426–e436.
104. Pengo V, Banzato A, Bison E, Zoppellaro G, Padayattil Jose S, Denas G. Efficacy and safety of rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome: rationale and design of the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) trial. *Lupus*. 2016;25:301–306.
105. Woller SC, Stevens SM, Kaplan DA, Branch DW, Aston VT, Wilson EL, Gallo HM, Johnson EG, Rondina MT, Lloyd JF, Evans RS, Elliott CG. Apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome: study rationale and design (ASTRO-APS). *Clin Appl Thromb Hemost*. 2016;22:239–247.
106. Hermans C, Eeckhoudt S, Lambert C. Dabigatran etexilate (Pradaxa(R)) for preventing warfarin-induced skin necrosis in a patient with severe protein C deficiency. *Thromb Haemost*. 2012;107:1189–1191.
107. Cook RM, Rondina MT, Horton DJ. Rivaroxaban for the long-term treatment of spontaneous ovarian vein thrombosis caused by factor V leiden homozygosity. *Ann Pharmacother*. 2014;48:1055–1060.
108. Sasaki Y, Raita Y, Uehara G, Higa Y, Miyasato H. Carotid thromboembolism associated with nephrotic syndrome treated with dabigatran. *Case Rep Nephrol Urol*. 2014;4:42–52.
109. Dupree LH, Reddy P. Use of rivaroxaban in a patient with history of nephrotic syndrome and hypercoagulability. *Ann Pharmacother*. 2014;48:1655–1658.
110. Pincus KJ, Hynicka LM. Prophylaxis of thromboembolic events in patients with nephrotic syndrome. *Ann Pharmacother*. 2013;47:725–734.
111. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. *J Am Soc Nephrol*. 2007;18:2221–2225.
112. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI; Coordinating Committee. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol*. 2012;59:1413–1425.
113. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387–2394.
114. Sardar P, Chatterjee S, Herzog E, Nairooz R, Mukherjee D, Halperin JL. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. *Can J Cardiol*. 2014;30:888–897.
115. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation*. 2015;131:972–979.
116. Liesenfeld KH, Clemens A, Kreuzer J, Brueckmann M, Schulze F. Dabigatran treatment simulation in patients undergoing maintenance haemodialysis. *Thromb Haemost*. 2016;115:562–569.
117. Dias C, Moore KT, Murphy J, Ariyawansa J, Smith W, Mills RM, Weir MR. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *Am J Nephrol*. 2016;43:229–236.
118. Parasrampuria DA, Marbury T, Matsushima N, Chen S, Wickremasingha PK, He L, Dishy V, Brown KS. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. *Thromb Haemost*. 2015;113:719–727.
119. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, Song Y, Pursley J, Boyd RA, Frost C. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol*. 2016;56:628–636.
120. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol*. 2011;57:1339–1348.
121. Guo Y, Wang H, Zhao X, Zhang Y, Zhang D, Ma J, Wang Y, Lip GY. Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation. *Int J Cardiol*. 2013;168:4678–4684.
122. Fanola CL, Mooney D, Cowan AJ, Ko D, Sisson EK, Henault LE, Tripodis Y, Hylek EM. Incidence of severe renal dysfunction among individuals taking warfarin and implications for non-vitamin K oral anticoagulants. *Am Heart J*. 2017;184:150–155.
123. Boulet SL, Grosse SD, Thornburg CD, Yusuf H, Tsai J, Hooper WC. Trends in venous thromboembolism-related hospitalizations, 1994–2009. *Pediatrics*. 2012;130:e812–e820.
124. Attard C, van der Straaten T, Karlaftis V, Monagle P, Ignjatovic V. Developmental hemostasis: age-specific differences in the levels of hemostatic proteins. *J Thromb Haemost*. 2013;11:1850–1854.
125. Dietrich K, Stang L, van Ryn J, Mitchell LG. Assessing the anticoagulant effect of dabigatran in children: an in vitro study. *Thromb Res*. 2015;135:630–635.
126. Attard C, Monagle P, Kubitza D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. *Thromb Res*. 2012;130:804–807.
127. Nossair FF, Chan HHW, Gantioqui J, Atkinson HM, Berry LR, Chan AKC. In-vitro assessment of the effect of dabigatran on thrombosis of adult and neonatal plasma: comparisons using thromboelastography and microscopic visualization of fibrin clot structure. *Blood Coagul Fibrinolysis*. 2017;28:551–557.
128. Attard C, Monagle P, Kubitza D, Ignjatovic V. The in-vitro anticoagulant effect of rivaroxaban in neonates. *Blood Coagul Fibrinolysis*. 2014;25:237–240.
129. Halton JM, Lehr T, Cronin L, Lobmeyer MT, Haertter S, Belletrutti M, Mitchell LG. Safety, tolerability and clinical pharmacology of dabigatran etexilate in adolescents. An open-label phase IIa study. *Thromb Haemost*. 2016;116:461–471.
130. Ginsberg JS, Crowther MA. Direct oral anticoagulants (DOACs) and pregnancy: a plea for better information. *Thromb Haemost*. 2016;116:590–591.
131. Bapat P, Kedar R, Lubetsky A, Matlow JN, Aleksa K, Berger H, Koren G. Transfer of dabigatran and dabigatran etexilate mesylate across the dually perfused human placenta. *Obstet Gynecol*. 2014;123:1256–1261.
132. Bapat P, Pinto LS, Lubetsky A, Berger H, Koren G. Rivaroxaban transfer across the dually perfused isolated human placental cotyledon. *Am J Obstet Gynecol*. 2015;213:710.e1–6.
133. Bapat P, Pinto LS, Lubetsky A, Aleksa K, Berger H, Koren G, Ito S. Examining the transplacental passage of apixaban using the dually perfused human placenta. *J Thromb Haemost*. 2016;14:1436–1441.
134. NIH. BEVYXXA—FDA full prescribing information (Reference ID: 4115694). 2017.
135. Beyer-Westendorf J, Michalski F, Tittl L, Middeldorp S, Cohen H, Abdul Kadir R, Arachchillage DJ, Arya R, Ay C, Marten S. Pregnancy outcome in patients exposed to direct oral anticoagulants—and the challenge of event reporting. *Thromb Haemost*. 2016;116:651–658.
136. Hoeltzenbein M, Beck E, Meixner K, Schaefer C, Kreutz R. Pregnancy outcome after exposure to the novel oral anticoagulant rivaroxaban in women

at suspected risk for thromboembolic events: a case series from the German Embryotox Pharmacovigilance Centre. *Clin Res Cardiol*. 2016;105:117–126.

137. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e691S–e736S.
138. Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. *Annu Rev Nurs Res*. 2000;18:48–90.
139. Waterman AD, Milligan PE, Bayer L, Banet GA, Gatchel SK, Gage BF. Effect of warfarin nonadherence on control of the International Normalized Ratio. *Am J Health Syst Pharm*. 2004;61:1258–1264.
140. Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *J Manag Care Pharm*. 2013;19:302–316.
141. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention for newly diagnosed and treatment-naive atrial fibrillation patients: an update using 2013–2014 data. *J Manag Care Spec Pharm*. 2017;23:958–967.
142. McHorney CA, Ashton V, Laliberte F, Germain G, Wynant W, Crivera C, Schein JR, Lefebvre P, Peterson ED. Adherence to rivaroxaban compared with other oral anticoagulant agents among patients with nonvalvular atrial fibrillation. *J Manag Care Spec Pharm*. 2017;23:980–988.
143. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. *N Engl J Med*. 2010;362:1553–1555.
144. Avorn J. The relative cost-effectiveness of anticoagulants: obvious, except for the cost and the effectiveness. *Circulation*. 2011;123:2519–2521.
145. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP; Investigators O-A and Patients. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II Registry. *J Am Coll Cardiol*. 2016;68:2597–2604.
146. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J*. 2016;37:1145–1153.
147. Basaran O, Dogan V, Beton O, Tekinalp M, Aykan AC, Kalaycioglu E, Bolat I, Tasar O, Safak O, Kalcik M, Yaman M, Inci S, Altintas B, Kalkan S, Kirma C, Biteker M; Collaborators. Suboptimal use of non-vitamin K antagonist oral anticoagulants: results from the RAMSES study. *Medicine (Baltimore)*. 2016;95:e4672.
148. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. *Am J Med*. 2016;129:1198–1204.
149. Tellor KB, Patel S, Armbruster AL, Daly MW. Evaluation of the appropriateness of dosing, indication and safety of rivaroxaban in a community hospital. *J Clin Pharm Ther*. 2015;40:447–451.

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