Advances in the Medical Management of Venous Thromboembolism

A review of the current data on VTE prevention and treatment using a variety of pharmacologic options.

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Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), continues to plague both hospitalized and nonhospitalized patients across all demographic and risk factor profiles. VTE represents the third most common cause of cardiovascular death after myocardial infarction and stroke. First-time occurrences are estimated to affect approximately 100 people per 100,000 annually[1] and, in total, between 100,000 and 300,000 patients per year in the United States alone.[2] In addition, despite wide-scale programs designed to prevent VTE, particularly in hospitalized patients, the incidence of VTE in the United States actually rose between 2002 and 2006 by about one-third.[3] The treatment of VTE is effective in preventing negative outcomes, but as in all other disease processes, the selection of the appropriate therapeutic agent and length of therapy is key and must be individualized to each clinical scenario.

RISK FACTORS FOR VTE

Acquired risk factors and noninherited thrombophilias account for the majority of VTE events. Risk factors for VTE include age, recent surgery (particularly orthopedic procedures), underlying malignancy, pregnancy, oral contraceptive use, and hormone replacement therapy.[4] Importantly, a previous episode of VTE significantly increases the risk of recurrence, regardless of whether the initial event was provoked. Hospitalization alone (for any indication) increases the risk of VTE by approximately eightfold.[5] Furthermore, common cardiovascular disease risk factors, such as hypertension, diabetes mellitus, obesity, and cigarette smoking, have been shown to increase the risk of VTE.[6] Inherited thrombophilias, such as factor V Leiden, protein C and S deficiency, and antiphospholipid antibody syndrome, also place patients at increased risk of thrombotic events. Despite recent advances in prevention and management, VTE remains a frequent cause of morbidity and mortality, particularly among patients who have been hospitalized.

MANAGEMENT OF VTE

During the past several decades, medical therapy for VTE was limited to heparin, warfarin, or their analogues. Despite the efficacy of both heparin agents and vitamin K antagonists (VKAs), such as warfarin, these agents have limitations, including narrow therapeutic windows, variability in individual patient pharmacodynamics, and the need for monitoring to ensure an adequate anticoagulant effect.[7,8] An aging patient population requiring anticoagulation for a variety of indications has increased the need for oral anticoagulants that offer the efficacy of VKAs with fewer logistical limitations. The following will review treatment guidelines for the management and prophylaxis of VTE in various subsets of patients, as well

as the literature regarding recent advances in the medical management of VTE.

DURATION OF THERAPY

The general duration of therapy for patients with VTE largely depends on the specific clinical scenario and whether the risk factors for VTE are transient or persistent. It is important to consider that despite anticoagulation therapy, approximately 6% of patients will have recurrent VTE during the first 6 months. Patients with provoked or unprovoked VTE will share similar risks of recurrence while receiving anticoagulant therapy. However, once anticoagulant therapy is stopped, those who have unprovoked VTE will have a higher recurrent risk of experiencing another event (specifically, approximately 10% at 1 year and 30% at 5 years). Those who have known triggers for VTE will have lower recurrence rates (specifically, approximately 3% at 1 year and 10% at 5 years).[8]

Regardless of the actual risk of recurrence, the true concern is the increased mortality rate (3.6%–10%) associated with recurrent episodes of VTE.[9,10] Although there is certainly a diminished risk of recurrence in patients who are treated with prolonged courses of anticoagulation, this benefit must be weighed against the concurrent increased risk of bleeding. As a result of the variety of clinical scenarios, the duration of therapy depends on whether the VTE event is provoked.

Unprovoked (Idiopathic) VTE

The exact duration of therapy for unprovoked VTE remains undetermined. The 2012 guidelines from the American College of Chest Physicians recommend anticoagulation for at least 3 months after an episode of unprovoked VTE.[8] After 3 months of therapy, patients with unprovoked VTE should be re-evaluated for the need for further therapy. If the patient is at low risk of bleeding and is generally compliant with therapeutic regimens, extended anticoagulation for PE and proximal DVT is generally recommended. In contrast, patients with a second episode of unprovoked VTE should receive indefinite anticoagulation. The clinician can also choose to conduct surveillance testing via venous duplex ultrasound and/or D-dimer assessment to help guide the length of anticoagulation therapy.

Provoked (Secondary) VTE

Patients with provoked VTE have a lower risk of recurrence than those with unprovoked VTE. The American College of Chest Physicians guidelines recommend a duration of anticoagulation therapy for 3 months in these cases.[8] However, therapy may be extended if exposure to the risk factor persists, such as in patients with malignancy. Other risk factors include recent surgery (particularly orthopedic procedures), prolonged immobility, hospitalization, long-distance travel, recent trauma, pregnancy, and the use of oral contraceptives.[11,12]

With regard to anticoagulant options, unfractionated heparin, low-molecular-weight heparin (LMWH), VKAs, and novel oral anticoagulants (discussed later) can be used. In patients with cancer, data from the CLOT trial favor the initial use of LMWH over warfarin (for at least 6 months) followed by further anticoagulation if the cancer is still active.[13]

FURTHER TESTING TO GUIDE DURATION OF THERAPY

Given the relative uncertainty regarding the optimal duration of therapy, clinicians have additional tools sanctioned by the current evidence that may be beneficial in guiding the duration of anticoagulation.

D-Dimer Testing

D-dimer testing has been evaluated as a means to assess the risk of developing recurrent VTE and thus the need for further anticoagulation.[14-16] The PROLONG study demonstrated that patients with an abnormal D-dimer value, measured 1 month out after an initial 3-month course of anticoagulation for unprovoked VTE, have higher rates of recurrence. Continuing anticoagulation in this cohort reduced this risk during an 18-month follow-up period.[17] The extended results of the PROLONG trial over a mean of 2.5 years showed that these results could be extrapolated over a longer time interval. Recurrent VTE rates were significantly higher in patients with an abnormal D-dimer level who were randomized not to resume anticoagulation than in those who resumed anticoagulation or in those with normal D-dimer values (23% vs 5% and 13%, respectively).[18]

Preliminary results from the PROLONG-PLUS trial suggest that D-dimer values could help guide therapy in patients with a history of multiple VTE events as well.[19] Pooled analysis of similar trials revealed that patients with negative D-dimer results have an annual risk for recurrent VTE of approximately 3.5%, whereas patients with a positive D-dimer result have an annual risk for recurrent VTE of approximately 8.9%.[20] With these results from PROLONG, clinicians can consider stopping anticoagulation after 3 months in patients who had their first episode of unprovoked VTE and a negative D-dimer. Further large-scale, randomized trials will be necessary to delineate the safety of relying on D-dimer values alone to direct the duration of therapy.

Venous Duplex Ultrasonography

The presence of residual thrombi on duplex venous ultrasonography has been shown to correlate with risk of recurrence,[21,22] and the positive predictive value of a stable or improved ultrasound study after an initial proximal DVT event is estimated to be approximately 90%.[23] Recent randomized trials have had promising results using repeat ultrasonography to help guide the duration of anticoagulation. Using the information garnered from ultrasound to guide therapy, Prandoni and colleagues demonstrated a 35% reduction in the risk of recurrent VTE events in 538 patients with a first episode of unprovoked proximal DVT, compared to conventional fixed dosing regimens, with no statistically significant increase in bleeding risk.[24] There is no formalized recommendation regarding how to use ultrasonography to guide therapeutic regimens in patients diagnosed with VTE. Thus, each patient's risk factor profile and clinical scenario should be used to decide the need for further imaging. Nevertheless, repeat duplex ultrasonography is yet another tool to guide the decision regarding the optimal duration of anticoagulation.

NOVEL CONCEPTS IN THE MEDICAL MANAGEMENT OF VTE

Statins and VTE

Already the mainstays in the medical management and prevention of cardiovascular disease, statins have also been touted for VTE prevention.[25,26] Statins have been shown to possess antithrombotic properties, and as a result, their use in the treatment and prevention of venous thromboembolic events has gained traction.[27] A recent meta-analysis revealed an odds ratio of 0.81 (95% confidence interval [CI], 0.66–0.99) for the development of a first episode of VTE in patients on statin therapy compared to those who were not.[28] Analysis of outcomes data from the JUPITER trial, which included more than 17,000 nonhyperlipidemic patients with elevated C-reactive protein levels, revealed a 53% reduction in VTE events (hazard ratio [HR], 0.47; 0.21–1.03; $P = .05$) in patients randomized to 20 mg of rosuvastatin compared to those who received a placebo.[29] Systematic reviews have since solidified the validity of the results from the JUPITER trial.[30]

Despite the beneficial aspect of utilizing statins in the prevention of VTE, the number needed to treat to prevent one VTE event has been estimated to be about 2,000, sparking some trepidation regarding the regular use of statins solely for the prevention of VTE.[31] A recent trial using registry data from the Netherlands examining the effect of statin therapy on the prevention of VTE in patients with previous PE revealed that statins were associated with a 50% reduction in the rate of recurrent PE (after adjustment for VKA therapy, sex, and history of cardiovascular disease events; HR, 0.5; 95% CI, 0.36–0.7). There was also a significant reduction in all-cause mortality, with greater benefit being derived from higher doses of statin therapy.[32] Although further studies must be performed to elucidate the mechanism whereby statins reduce VTE risk, current data suggest that statins are as safe and effective as adjunctive therapy for both primary and secondary prevention of VTE events.

Aspirin and VTE

In the past 30 years, aspirin has been evaluated for a multitude of cardiovascular disease processes, including the prevention of VTE. The WARFASA trial demonstrated that compared to placebo, aspirin at a dose of 100 mg daily reduced the risk of recurrent VTE following 6 to 18 months of VKA therapy in patients with initial episodes of unprovoked VTE (6.6% vs 11.2% per year; HR, 0.58; 95% CI, 0.36–0.93) over a follow-up of about 2 years with no significant increase in bleeding risk.[33] The ASPIRE trial of more than 800 postoperative patients revealed a 34% reduction in the composite secondary outcome of VTE, myocardial infarction, stroke, or cardiovascular death with aspirin (HR, 0.66; 95% CI, 0.48–0.92; $P = .01$), due mainly to a reduced incidence of arterial ischemic events. However, the rate of recurrent VTE was not statistically significant.[34] Although still controversial, these studies suggest that in selected patients, aspirin at doses of 100 mg daily or higher following at least 3 months of traditional anticoagulation may be a viable option for preventing recurrent venous, as well as arterial, thromboembolic events, with a minimal increased risk of bleeding.

Low-Intensity Warfarin

Moderate-intensity VKA therapy with a goal international normalized ratio (INR) of 2 to 3 remains the standard of care in the management of VTE. There is debate, however, as to whether so-called low-intensity anticoagulation with a goal INR of 1.5 to 2 is efficacious and has a theoretically lower risk of bleeding. Two pivotal trials tackled these questions in the early to mid 2000s: the PREVENT and ELATE trials. The PREVENT trial randomized about 500 patients with unprovoked PE or DVT who had completed an average of 6 months of anticoagulation to either placebo or low-intensity warfarin with a target INR of 1.5 to 2. Patients in the warfarin group had an approximately two-thirds lower rate of recurrence compared to the placebo group. The study was terminated early at 2 years as a result of the overwhelmingly positive results in the warfarin group. Furthermore, there

was no statistically significant difference between the two groups in terms of bleeding risk.[35]

The Canadian ELATE trial, however, had opposite results. The trial compared low-intensity warfarin to standard warfarin therapy (INR goal, 2–3) in about 740 patients who were previously treated for unprovoked VTE. During an approximately 2-year follow-up period, the likelihood of recurrence was about three times higher in the low-intensity cohort compared to the standard-intensity group, with no significant difference in terms of major adverse event rates.[14] Although more studies are certainly needed, the data imply that even though low-intensity warfarin is better than placebo, standard anticoagulation remains optimal for long-term secondary prevention of unprovoked VTE.[36]

NOVEL ORAL ANTICOAGULANTS

Novel oral anticoagulants have been developed over the past decade, partially in response to the flaws inherent to traditional anticoagulation for VTE, including variations in patient response to therapy as well as the need for routine monitoring. These agents generally have one of two mechanisms: inhibition of coagulation factor IIa (thrombin) or of factor Xa. The following is a brief review of the evidence behind the use of the novel oral agents for the management of VTE and the strategies for selecting the optimum oral anticoagulant in a variety of clinical scenarios.[37,38] For a more detailed review of the clinical trial data for the use of novel oral anticoagulants in comparison with conventional anticoagulation strategies for VTE, we recommend

TABLE 1. PHARMACOLOGIC PROPERTIES OF SELECTED NOVEL ORAL ANTICOAGULANTS[a]

	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Direct thrombin (IIa) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Metabolism and excretion	80% renal, 20% fecal	66% renal, 33% fecal	27% renal, 73% fecal or biliary
Protein binding	35%	92%–95%	87%
Half-life	12–17 h	5–9 h	8–15 h
Oral bioavailability	3%–7%	10 mg: 80%–100%; 20 mg: 66%	50%
Time to peak effect	1–3 h	1–3 h	1–3 h
Dosing (VTE prophylaxis)	Normal renal function: initiate at 110 mg (1–4 h after surgery), continue at 220 mg for 28–35 d; abnormal renal function (creatinine clearance < 50 mL/min): initiate at 75 mg, continue at 150 mg daily for 28–35 d	Initiate at 10 mg (6–10 h after surgery), continue at 10 mg daily for 12 d (knee surgery) or 25 d (hip surgery)	Initiate at 2.5 mg twice daily (12–24 h after surgery), continue at 2.5 mg twice daily for 10–14 d (knee surgery) or 32–38 d (hip surgery)
Dosing (VTE therapy)	Not currently approved	Acute VTE: 15 mg twice daily for 3 wk followed by 20 mg/d for treatment period; extended therapy: after an initial 6 mo of anticoagulation, 20 mg daily	Not currently approved
Monitoring	Not required	Not required	Not required
Antidote	None	None	None
Drug interactions	P-glycoprotein	CYP3A4	CYP3A4, P-glycoprotein

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the recent article by Makaryus et al in *Nature Reviews Cardiology*.[39]

Dabigatran

Dabigatran is a direct thrombin inhibitor that has a half-life of approximately 12 to 17 hours (Table 1). Approximately 80% of the drug is renally cleared, and thus, caution is advised in patients with renal insufficiency.

VTE prophylaxis. Three randomized clinical trials have established the efficacy of dabigatran for VTE prophylaxis (Table 2). The RE-MODEL and RENOVATE I and II trials established the noninferiority of dabigatran compared to enoxaparin for the prevention of VTE in patients undergoing orthopedic surgery. In general, dabigatran was found to be equivalent to standard therapy at preventing the composite outcome of VTE events and all-cause mortality, with no significant difference in terms of bleeding risk.[40] The RE-MOBILIZE trial, which compared dabigatran to enoxaparin (30 mg subcutaneously twice daily) in knee replacement surgery failed to demonstrate the noninferiority of dabigatran in preventing the same endpoint.[41] Nevertheless, most data point to similar effi-

TABLE 2. PHASE III CLINICAL TRIALS OF DABIGATRAN FOR VTE PROPHYLAXIS AND THERAPY[a]

VTE Prophylaxis

Trial	Patient Population/ Cohort Size	Dabigatran Dose/ Duration	Enoxaparin Dose/ Duration	DVT/PE/ Death (%) Dabigatran Versus Enoxaparin	*P* Value	Major Bleeding (%) Dabigatran Versus Enoxaparin	*P* Value
RE-MODEL	TKR n = 2,101	150 or 220 mg daily for 6–10 d	40 mg daily for 6–10 d	40.5% (150 mg), 36.4% (220 mg) vs 37.7%	.82 (150 mg), .38 (220 mg)	1.3% (150 mg), 1.5% (220 mg) vs 1.3%	1 (150 mg), .82 (220 mg)
RE-NOVATE	THR n = 3,493	150 or 220 mg daily for 28–35 d	40 mg daily for 28–35 d	8.6% (150 mg), 6% (220 mg) vs 6.7%	< .0001 (150 mg), < .0001 (220 mg)	1.3% (150 mg), 2% (220 mg) vs 1.6%	.6 (150 mg), .44 (220 mg)
RE-NOVATE II	THR n = 2,055	220 mg daily for 28–35 d	40 mg daily for 28–35 d	7.7% vs 8.8%	< .0001	1.4% vs 0.9%	.4
RE-MOBILIZE	TKR n = 2,615	150 or 220 mg daily for 12–15 d	30 mg twice daily for 12–15 d	33.7% (150 mg), 31.1% (220 mg) vs 25.3%	.0009 (150 mg), .0234 (220 mg)	0.6% (150 mg), 0.6% (220 mg) vs 1.4%	N/A

VTE Therapy

Trial	Patient Population/ Cohort Size	Study Design	Recurrent VTE	*P* Value	Major Bleeding
RE-COVER	2,539 patients with acute VTE initially treated with parenteral anticoagulation (median, 9 d)	Randomized, double-blind, noninferiority trial of dabigatran 150 mg twice daily vs warfarin	Dabigatran 150 mg twice daily: 30/1,274 (2.4%); warfarin: 27/1,265 (2.1%)	< .001 (noninferiority)	Dabigatran: 20/1,274 (1.6%); warfarin: 24/1,265 (1.9%)

Abbreviations: THR, total hip replacement; TKR, total knee replacement.

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TABLE 3. CURRENT APPROVED CLINICAL USE OF NOVEL ORAL ANTICOAGULANTS[a]

	Nonvalvular AF		VTE Prophylaxis After Orthopedic Surgery		Acute VTE Treatment		Extended VTE Therapy	
	US FDA	Canada/ Europe	US FDA	Canada/ Europe	US FDA	Canada/ Europe	US FDA	Canada/ Europe
Dabigatran	✓	✓		✓				
Rivaroxaban	✓	✓	✓	✓	✓	✓	✓	✓
Apixaban	✓	✓		✓				

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cacies of dabigatran and standard anticoagulation with similar safety profiles.

VTE therapy. The RE-COVER trial enrolled patients with acute PE or proximal DVT and compared long-term therapy with warfarin to dabigatran following initial therapy with LMWH (Table 2). This double-blind, randomized, noninferiority study showed dabigatran to be noninferior to warfarin for preventing the primary outcome of 6-month incidence of recurrent VTE or VTE-related deaths, with a higher overall rate of bleeding in the warfarin group, although this difference was nonsignificant.[42]

The efficacy and safety of dabigatran in the secondary prevention of VTE was studied in the RE-MEDY and RE-SONATE trials, comparing dabigatran to warfarin and placebo in the prevention of recurrent symptomatic VTE (Table 2).[43] Recently released data from these trials have shown dabigatran to be effective in the extended treatment (following at least 3 months of traditional anticoagulant therapy) of VTE compared to warfarin (HR with dabigatran, 1.44; 95% CI, 0.78–2.64; $P = .01$ for noninferiority) and compared to placebo (HR, 0.08; 95% CI, 0.02–0.25; $P < .001$), with similar rates of major bleeding episodes. Based on the evidence available to date, dabigatran appears at least as effective as warfarin, with a similar risk factor profile for treating patients with established VTE.[44]

Dosing recommendations. Dabigatran has not yet received approval for any VTE indication in the United States (Table 3). In countries where the drug has been approved for VTE prophylaxis following orthopedic surgery, dabigatran is first given at a dose of 110 mg within 4 hours after surgery, continued at a daily dose of 220 mg, and then for a total of approximately 10 days after knee arthroplasty and 28 to 35 days after hip arthroplasty. For patients with moderate to severe renal insufficiency, older than 75 years, or those taking medications that inhibit P-glycoproteins, a lower dose of 75 mg daily is recommended (Table 1). Dabigatran has not yet received approval for treatment of acute VTE.

Rivaroxaban

Rivaroxaban was the first commercially available oral factor Xa inhibitor. The drug has a half-life of 5 to 9 hours, with one-third cleared by the kidneys and the remainder by the hepatobiliary system (Table 1).[45] The US Food and Drug Administration (FDA) approved rivaroxaban for the prevention of VTE after orthopedic surgery, for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF),[46] to treat patients with DVT and/or PE, and to reduce the risk of recurrent DVT and PE (Table 3). Like dabigatran, rivaroxaban should be used with caution in patients with underlying renal insufficiency, with dose reduction recommended if a patient's creatinine clearance is between 30 and 50 mL/min. Rivaroxaban should not be used if the creatinine clearance is below 30 mL/min (Table 4).

VTE prophylaxis. The utility of rivaroxaban in the management of VTE was primarily established by the RECORD trials (Table 5). These four trials demonstrated that rivaroxaban 10 mg once daily compared favorably to enoxaparin regimens administered after orthopedic surgery, with a pooled relative risk of VTE of 0.38 with rivaroxaban compared to enoxaparin, 40 mg subcutaneously daily ($P < .0001$) and 0.77 compared to enoxaparin, and 30 mg subcutaneously twice daily ($P = .05$) with similar adverse event rates.[47]

TABLE 4. CONTRAINDICATIONS AND WARNINGS FOR SELECTED NOVEL ORAL ANTICOAGULANTS[a]

Dabigatran	**Contraindications**	**Warnings/Precautions**
	• Bleeding • Hypersensitivity	• Concomitant use of P-glycoprotein inducers or inhibitors • Renal insufficiency • Prosthetic heart valves • Pregnancy (category C)
Rivaroxaban	• Bleeding • Hypersensitivity	• Concomitant use of P-glycoprotein inducers or inhibitors • Concomitant use of strong CYP34A inhibitors • Avoid if creatinine clearance < 30 mL/min • Avoid in patients with hepatic impairment • Prosthetic heart valves • Pregnancy (category C)
Apixaban	• Bleeding • Hypersensitivity	• Concomitant use of P-glycoprotein inducers or inhibitors • Concomitant use of strong CYP34A inhibitors • Renal insufficiency • Avoid in patients with hepatic impairment • Prosthetic heart valves • Pregnancy (category B)

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Extended therapy with rivaroxaban compared to enoxaparin in medically ill patients was evaluated in the MAGELLAN trial (Table 5). The MAGELLAN trial showed rivaroxaban to be noninferior to enoxaparin in preventing symptomatic VTE or asymptomatic proximal DVTs, with a relative risk for rivaroxaban of 0.77 (95% CI, 0.62–0.96; *P* = .02 for noninferiority) after 35 days. Unlike the RECORD trials, however, MAGELLAN results showed an increased risk of bleeding in patients taking rivaroxaban over the short-term period of follow-up (4.1% and 1.7% at day 35, respectively; *P* < .001).[29]

VTE therapy. With regard to the treatment of diagnosed VTE, the EINSTEIN-DVT trial compared rivaroxaban—15 mg twice daily for 3 weeks followed by 20 mg once daily for 3, 6, or 12 months—and LMWH or VKA in patients with DVT without symptomatic PE.[41] The incidence of recurrent symptomatic VTE was 3% in the conventional therapy arm compared to 2.1% in the rivaroxaban arm (HR, 0.68; 95% CI, 0.44–1.04; noninferiority *P* < .0001), with similar bleeding rates between both groups.[48]

EINSTEIN-PE, focusing on patients with symptomatic acute PE,[49] revealed rivaroxaban to be noninferior to LMWH and VKA (noninferiority margin, 2; *P* = .003) for the prevention of recurrent VTE (HR, 1.12; 95% CI, 0.75–1.68), although there were more major bleeding events within the rivaroxaban group (HR, 0.49; 95% CI, 0.31–0.79; *P* = .003), implying that a fixed-dose regimen of rivaroxaban may be safer.[49,50] For extended prevention of VTE recurrence, the EINSTEIN-Extension trial found rivaroxaban to be more effective than placebo, with an 82% relative risk reduction (*P* = .001) and a major bleeding incidence of 0.7% in the rivaroxaban group and none within the placebo group.[48,51]

Dosing recommendations. For VTE prophylaxis, rivaroxaban can be given at 10 mg daily for approximately 12 days following knee surgery and 25 days following hip replacement surgery. The drug was recently granted FDA approval for the treatment of acute VTE at 15 mg twice daily for 3 weeks followed by 20 mg daily for the remainder of the treatment period.

Apixaban

Another direct factor Xa inhibitor, apixaban, is being used for an increasing number of indications. The drug has a half-life of 8 to 15 hours (Table 1). Given its primarily fecal route of elimination, apixaban may be better tolerated in patients with renal insufficiency, although it may be generally advisable to consider VKAs in patients with advanced chronic kidney disease.[52] In Canada and Europe, apixaban is approved for the primary prevention of VTE in patients undergoing orthopedic surgery

TABLE 5. PHASE III CLINICAL TRIALS OF RIVAROXABAN FOR VTE PROPHYLAXIS AND THERAPY[a]

VTE Prophylaxis

Trial	Patient Population/ Cohort Size	Rivaroxaban Dose/Duration	Enoxaparin Dose/ Duration	DVT/PE/ Death (%) Rivaroxaban Versus Enoxaparin	*P* Value	Major Bleeding (%) Rivaroxaban Versus Enoxaparin	*P* Value
RECORD 1	THR n = 4,501	10 mg daily/35 d	40 mg daily/35 d	1.1% vs 3.7%	< .001	0.3% vs 0.1%	.18
RECORD 2	THR n =2,509	10 mg daily/31–39 d	40 mg daily/14 d	2% vs 9.3%	< .0001	< 0.1% vs <0.1%	–
RECORD 3	TKR n = 2,615	10 mg daily/10–14 d	40 mg daily/10–14 d	9.6% vs 18.9%	< .001	0.6% vs 0.5%	.77
RECORD 4	TKR n = 2,055	10 mg daily/10–14 d	40 mg twice daily/10–14 d	6.9% vs 10.1%	.0118	0.7% vs 0.3%	.11
MAGELLAN	Acute medical illness n = 8,101	10 mg daily/35 ± 4 d	40 mg daily/10 ± 4 d	2.7% vs 2.7%	.003	2.8% vs 1.2%	.001

VTE Therapy

Trial	Patient Population/ Cohort Size	Study Design	Symptomatic Recurrent VTE	*P* Value	Major Bleeding (%) Apixaban Versus Enoxaparin
Einstein-DVT	3,448 patients with acute symptomatic DVT	Noninferiority study of rivaroxaban alone (15 mg twice daily for 3 wk followed by 20 mg daily) vs enoxaparin followed by a VKA for 3, 6, or 12 mo	Rivaroxaban: 36 events (2.1%); enoxaparin + VKA: 51 events (3%)	< .001 (noninferiority)	Rivaroxaban: 8%; enoxaparin/VKA: 8%
Einstein-PE	4,832 patients with acute symptomatic PE ± DVT	Noninferiority study of rivaroxaban (15 mg twice daily for 3 wk followed by 20 mg daily) vs enoxaparin followed by a VKA for 3, 6, or 12 mo	Rivaroxaban: 50 events (2.1%); enoxaparin + VKA: 44 events (1.8%)	.003 (noninferiority)	Rivaroxaban: 10.3%; enoxaparin/VKA: 11.4%; (*P* = .23)
Einstein-EXT	1,196 patients who completed 6–12 mo anticoagulation for VTE	Double-blind superiority study of rivaroxaban alone (15 mg twice daily for 3 wk followed by 20 mg daily) vs enoxaparin followed by a VKA for 6–12 mo	Rivaroxaban: 8 events (1.3%); placebo: 42 events (7.1%)	< .001	Rivaroxaban: 0.7%; enoxaparin/VKA: 0%; (*P* = .11)

Abbreviations: THR, total hip replacement; TKR, total knee replacement.

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TABLE 6. PHASE III CLINICAL TRIALS OF APIXABAN FOR VTE PROPHYLAXIS AND THERAPY[a]

VTE Prophylaxis

Trial	Patient Population/ Cohort Size	Apixaban Dose/ Duration	Enoxaparin Dose/ Duration	DVT/PE/ Death (%) Apixaban Versus Enoxaparin	*P* Value	Major Bleeding (%) Apixaban Versus Enoxaparin	*P* Value
ADVANCE-1	TKR n = 3,195	2.5 mg twice daily for 10–14 d	30 mg twice daily for 12 d	Apixaban failed noninferiority to enoxaparin: 9% vs 8.8%	.06 (noninferiority)	0.7% vs 1.4%	.05
ADVANCE-2	TKR n = 3,057	2.5 mg twice daily for 10–14 d	40 mg daily for 10–14 d	15.1% vs 24.4%	< .0001 (superiority)	0.6% vs 0.9%	.3
ADVANCE-3	THR n = 5,407	2.5 mg twice daily for 35 d	40 mg daily for 35 d	1.4% vs 3.9%	< .001 (superiority)	0.8% vs 0.7%	.54
ADOPT	Medical illness n = 4,495	2.5 mg twice daily for 30 d	40 mg twice daily for 6–14 d	2.71% vs 3.06%	.44	0.46% vs 0.19%	.04

VTE Therapy

Trial	Patient Population/ Cohort Size	Study Design	DVT/PE/Death (%)	*P* Value	Major Bleeding (%)
AMPLIFY	5,395 acute VTE patients: apixaban (n = 2,609); conventional therapy (enoxaparin/ warfarin [n = 2,635])	Randomized, double-blinded trial	Apixaban: 59/2,609 (2.3%); conventional therapy: 71/2,635 (2.7%)	< .001 (noninferiority)	Apixaban: 0.6%; conventional therapy: 1.8% (*P* < .001 for superiority)
AMPLIFY-EXT	2,482 VTE completed 6–12 mo of therapy	ITT analysis of apixaban 2.5 mg twice daily or 5 mg twice daily vs placebo	Apixaban (2.5 mg): 14/830 (1.7%); Apixaban (5 mg): 14/813 (1.7%); placebo: 73/829 (8.8%)	< .001 (superiority)	Apixaban (2.5 mg): 0.2%; apixaban (5 mg): 0.1%; placebo: 0.5%

Abbreviations: ITT, intention to treat; THR, total hip replacement; TKR, total knee replacement.

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(Table 3). The FDA has yet to grant approval for apixaban in VTE prophylaxis or treatment.

VTE prophylaxis. The ADVANCE trials evaluated apixaban for the prevention of VTE in patients undergoing orthopedic surgery. Although ADVANCE-1 failed to demonstrate the noninferiority of apixaban in preventing the composite outcome of nonfatal PE, DVT, and all-cause mortality,[53] apixaban compared favorably to standard therapy with enoxaparin in the following two trials, which showed apixaban to be noninferior (ADVANCE-2) and even superior (ADVANCE-3) to enoxaparin.[54,55] In both studies, the rates of major bleeding were similar in the two treatment arms (Table 6).

For extended prophylaxis, the ADOPT trial compared prophylaxis with apixaban for 30 days compared to short-term prophylaxis with enoxaparin for 6 to 14 days in acutely ill patients. The trial demonstrated no statistically significant difference between the two groups in terms of VTE events, although there was a statistically significant increase in the risk of major bleeding in the apixaban group compared to the enoxaparin group at 30 days (risk ratio, 2.58; 95% CI, 1.02–7.24; *P* = .04) (Table 6).[56] The results of these studies support the use of oral fac-

tor Xa inhibitors to prevent VTE over a standard period of time, without increasing the risk of bleeding compared to conventional anticoagulation strategies. Further studies are needed to determine the potential utility of extended prophylaxis with these agents.

VTE treatment. Apixaban has been studied for the treatment of diagnosed VTE as well. Recently published results from the AMPLIFY trial demonstrated that a fixed-dose regimen of apixaban was noninferior to conventional therapy composed of enoxaparin followed by warfarin ($P < .001$). The primary efficacy outcome of symptomatic recurrent VTE or VTE-related death was reached in 2.3% of the patients in the apixaban group versus 2.7% in the conventional therapy group. Of note, apixaban was associated with significantly less bleeding, as major bleeding occurred in 0.6% versus 1.8% (apixaban vs conventional therapy), respectively (risk ratio, 0.31; 95% CI, 0.17–0.55, $P < .001$ for superiority). Apixaban also compared more favorably against conventional therapy when evaluating the composite outcome of major bleeding and clinically relevant nonmajor bleeding (4.3% vs 9.7%, respectively; $P < .001$) (Table 6).[57] The companion trial, AMPLIFY-EXT (Extension),[58] is an intention-to-treat analysis, which revealed that either 2 or 5 mg of apixaban effectively reduced the risk of recurrent VTE, without an increased risk of bleeding, when compared to placebo (1.7% incidence of recurrent VTE or VTE-related death in both treatment groups compared to 8.8% of the placebo group).[58] Furthermore, the rates of major bleeding were actually lower in the treatment groups, with comparable nonmajor bleeding rates in all three cohorts.

Dosing recommendations. For VTE prophylaxis, apixaban is given at 2.5 mg twice daily, which is started within 24 hours of surgery. The recommended duration of therapy is 10 to 14 days after knee replacement and 32 to 38 days after hip replacement surgeries. Apixaban has not yet received approval for acute VTE treatment (Table 3).

Other Agents

Numerous anticoagulants are currently under investigation for a wide array of indications. Edoxaban, another factor Xa inhibitor, has been approved in Japan for VTE prevention following lower limb surgery and is under investigation for the prevention of stroke and systemic embolism in patients with AF in the ENGAGE-AF trial.[59] Other agents, including betrixaban[60] and otamixaban,[61] are currently in earlier stages of development. The utility of these two agents in the prevention and management of VTE is as yet unknown.

CONCLUSION

The prevention and management of VTE has progressed significantly over the past decade. Although heparin analogues and vitamin K antagonists were, and remain, the mainstay of therapy, the last few years have seen a dramatic increase in the number of novel agents such as dabigatran, rivaroxaban, and apixaban being used in the management of the disease. This has largely been driven by the need for a more predictable therapeutic effect, ease of administration, and the need to minimize adverse outcomes. More research on these and other new agents, in addition to further analysis of treatment algorithms that incorporate diagnostic modalities including venous duplex ultrasonography and D-dimer levels, should help tailor the clinician's approach toward the prevention and management of VTE. ■

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