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The New Oral Anticoagulants for the Treatment of Venous Thromboembolism: A New Paradigm Shift in Antithrombotic Therapy



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ABSTRACT

Background: Several novel oral anticoagulants have been studied for the prevention and treatment of venous thromboembolism (VTE) in different patient populations. Clinicians will increasingly encounter scenarios in which they must choose among these and conventional anticoagulants for the treatment of this potentially fatal condition.

Objective: To review the results of Phase III clinical trials that investigated the novel oral anticoagulants for the treatment of deep vein thrombosis and pulmonary embolism. Potential advantages and disadvantages of these anticoagulant agents with respect to each other and conventional therapy will also be explored through a case-based approach.

Methods: A literature search in PubMed was conducted that identified Phase III clinical trials investigating the novel oral anticoagulant agents for the treatment of VTE.

Results: The new oral anticoagulant agents have been shown to be as safe and effective for the treatment of VTE as conventional therapies.

Conclusions: These novel, oral anticoagulant agents are legitimate options for the treatment of VTE. A careful assessment of a patient's comorbidities, medication use, and laboratory results should be undertaken before prescribing the new oral anticoagulant agents for patients with VTE.

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Several novel, oral anticoagulant agents have been studied for the prevention and treatment of venous thromboembolism (VTE). The purpose of this article is to review the results of Phase III clinical trials that investigated these medications for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Potential advantages and disadvantages of these anticoagulant agents with respect to each other and conventional therapy will also be explored through a case-based approach.

Pharmacologic Profile

The pharmacologic profile of the new oral anticoagulants is summarized in [Table 1](#). These medications share similar properties, such as quick onset of action, interactions with the P-glycoprotein pathway, and renal excretion. All of the Phase III clinical trials excluded patients with severe renal insufficiency,

including the dialysis population. Unlike the factor Xa inhibitors, dabigatran is neither a substrate nor an inhibitor/inducer of the cytochrome P450 system. Because of its lower protein binding, dabigatran is partially dialyzable, whereas the other anticoagulants cannot be eliminated via this mechanism. There is no currently available antidote for any of these medications and the reversal of their anticoagulant effects with products such as prothrombin complex concentrate and fresh frozen plasma has been minimally investigated.¹ Furthermore, there are no validated tests to monitor the anticoagulant effects of these medications because they were specifically studied in Phase III trials without the need to perform routine monitoring. The thrombin clotting time, ecarin clotting time, and activated partial thromboplastin time are most affected by dabigatran and may be useful for ruling out the presence or absence of its anticoagulant effect.² Apixaban, rivaroxaban, and edoxaban prolong the prothrombin time to a greater extent than the activated partial thromboplastin time.^{3,4} As will be shown below, the trials investigating these anticoagulants for the treatment of VTE are divided into 2 basic groups. In the acute VTE studies, the novel anticoagulants were compared with standard therapy in patients with a new VTE who were not being treated with any anticoagulation at the time of the diagnosis.

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Table 1
Pharmacologic profile of the new oral anticoagulants.

Variable	Apixaban	Dabigatran etexilate ^a	Rivaroxaban	Edoxaban
Target	Factor Xa	Factor IIa (thrombin)	Factor Xa	Factor Xa
Bioavailability (%)	50	7	10 mg dose: 80–100 20 mg dose: 66 (increases with food)	60
Time to peak onset (h)	3–4	1	2–4	1–2
Half-life (h)	12	12–17	5–9	8–10
Metabolism	~25% Hepatic (CYP3A4) ~75% Unchanged	~20% Conjugation ~80% Unchanged	~50% Hepatic (CYP3A4/5, CYP212) ~50% Unchanged	~30% (Hydrolysis, CYP3A4) ~70% Unchanged
Elimination	~25% Renal ~75% Intestinal	~80% Renal ~80% Intestinal	~66% Renal ~28% Intestinal	~35% Urine ~65% Intestinal
P-glycoprotein interaction [†]	Yes	Yes	Yes	Yes
Cytochrome P450 interaction	Yes	No	Yes	Yes
Coagulation tests most affected	PT/INR, anti-factor Xa activity	aPTT, ECT, TT	PT/INR, anti-factor Xa activity	PT/INR, anti-factor Xa activity
Dialyzable	No	Yes (60%)	No	No
Antidote	No	No	No	No

aPTT = activated partial thromboplastin time; ECT = ecarin clotting time; PT/INR = prothrombin time/international normalized ratio; TT = thrombin clotting time.

^a Dabigatran etexilate is hydrolyzed by hepatic and plasma esterases to dabigatran.

[†] The P-glycoprotein (P-gp) system prevents the absorption or enhances the secretion of certain medications known as P-gp substrates. Inhibition of this system increases the drug levels of P-gp substrates whereas its induction decreases drug levels. Apixaban, dabigatran, and rivaroxaban are P-gp substrates.

In the extended treatment studies, patients who completed at least a 3-month duration of treatment for a VTE were randomized to various therapies.

Clinical Trial Results for Acute VTE

Rivaroxaban

Two trials investigated the use of rivaroxaban for the treatment of VTE. The Einstein-Acute DVT study was an open-label, randomized, event-driven, noninferiority trial comparing rivaroxaban (15 mg twice daily for the first 3 weeks followed by 20 mg once daily) to conventional anticoagulation therapy, which consisted of a low-molecular-weight heparin followed by a vitamin K antagonist, in patients with a proximal DVT without PE.⁵ Patients with a creatinine clearance < 30 mL/min, clinically significant liver disease, or severe hypertension were excluded. The use of a thrombectomy procedure, a vena cava filter, or fibrinolytic agents rendered patients ineligible for the trial. Concomitant use of strong cytochrome P450 inhibitors (ie, protease inhibitors or systemic ketoconazole) or inducers (ie, rifampicin, carbamazepine, and phenytoin) were also reasons for exclusion. The use of nonsteroidal anti-inflammatory agents or antiplatelet medications was allowed although discouraged. Specifically, aspirin up to a total daily dose of 100 mg, clopidogrel 75 mg/d, or both were permitted. The majority of patients were treated for 6 to 12 months. The primary efficacy outcome was symptomatic, recurrent VTE (including fatal PE), whereas the main safety measure was the combination of major or clinically relevant nonmajor bleeding. As shown in Table 2, rivaroxaban was as effective as standard therapy in preventing recurrent VTE with a similar safety profile.

Only 12% to 13% of patients in this study were older than age 75 years. Patients with a creatinine clearance of 30 mL/min were excluded; however, only 7% to 8% of patients had a creatinine clearance between 30 and 50 mL/min.⁵ Unlike the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial

Fibrillation (ROCKET-AF) study in which patients with a creatinine clearance between 30 and 50 mL/min were given a reduced dose of rivaroxaban 15 mg once daily, all patients in the Einstein-DVT study received the 20 mg daily dose regardless of kidney function. Sixty-eight percent to 70% of patients were considered to have an extensive thrombus burden. There were no differences in the efficacy outcome in the subgroup analysis according to the type of thrombotic event (idiopathic vs provoked), presence of thrombophilia or malignancy, or extent of thrombus burden. Rivaroxaban was not associated with an increase in risk of vascular events, changes in liver function tests, or premature discontinuation of study drug compared with standard therapy.

The Einstein-PE trial was an open-label, event-driven, noninferiority study with a similar design to the Einstein-acute DVT trial comparing rivaroxaban with standard therapy in patients with a PE (with or without a DVT). The principal efficacy outcome and safety measure were the same as in the Einstein-DVT trial.⁶ The majority of patients were treated for 6 to 12 months. A dose-confirmation phase was performed in which the first 400 patients underwent repeat lung imaging at the end of the first 3 weeks of treatment to exclude asymptomatic deterioration. There was no difference in the efficacy outcome at the end of the first 21 days of therapy. Overall, rivaroxaban was found to be as effective and safe as standard therapy in preventing recurrent VTE. Significantly less major bleeding occurred in patients treated with rivaroxaban. Approximately 24% to 25% of patients in the trial were considered to have extensive thrombus burden as defined by the involvement of multiple lobes and > 25% of the entire pulmonary vasculature. There were no differences in the efficacy outcome according to thrombus burden or type of index event. There were also no differences in changes of liver function parameters, coronary events, or premature discontinuation of study drug between the groups.

A pooled analysis of the Einstein trials was recently published⁷ that verified the noninferiority of rivaroxaban compared with vitamin K antagonism. That analysis also revealed a statistically significant reduction in major bleeding in patients exposed to this anti-Xa inhibitor compared with the conventional anticoagulation

Table 2
Clinical trials comparing the new oral anticoagulants with standard therapy in acute venous thromboembolism.*

Variable	Einstein-DVT	Einstein-PE	AMPLIFY [€]	RE-COVER	RE-COVER II	Hokusai-VTE
Trial design	Open-label, randomized	Open-label, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized
Regimen	Rivaroxaban 15 mg BID × 3 wk, then 20 mg daily	Rivaroxaban 15 mg BID × 3 wk, then 20 mg daily	Apixaban 10 mg BID × 7 d, then 5 mg BID	Standard therapy for median 9 d, then dabigatran 150 mg BID	Standard therapy for median 9 d, then dabigatran 150 mg BID	Standard therapy for median 7 d, then edoxaban 60 mg daily (30 mg daily if CrCL 30–50 mL/min or weight ≤ 60 kg)
Average age (y)	55–58	58	57	54–55	55	56
PE only (%)	—	All patients	25	21	23	30
DVT + PE (%)	All patients (no PE)	25	8–9	10	8–9	10
Unprovoked VTE (%)	61–63	64–65	90	Undefined	Undefined	65–66
Prior VTE (%)	19	19–20	15–17	25–26	16–19	65–66
Malignancy (%)	5–7	5	3	5	4	9
Thrombophilia (%)	6–7	5–6	2–3	Undefined	Undefined	Undefined
%TTR for INR [†] (%)	57.7	62.7	61	60	57	63.5%
Efficacy outcome [‡]	Rivaroxaban: 2.1% Standard Tx: 3.0%	Rivaroxaban: 2.1% Standard Tx: 1.8%	Apixaban: 2.3% Standard Tx: 2.7%	Dabigatran: 2.4% Standard Tx: 2.1%	Dabigatran: 2.3% Standard Tx: 2.2%	Edoxaban: 3.2% Standard Tx: 3.5%
Major bleeding [§]	Rivaroxaban: 0.8% Standard Tx: 1.2%	Rivaroxaban: 1.1% Standard Tx: 1.2%	Apixaban: 0.6% Standard Tx: 1.8%	Dabigatran: 1.6% Standard Tx: 1.9%	Dabigatran: 1.2% Standard Tx: 1.7%	Edoxaban: 1.4% Standard Tx: 1.6%
Clinically relevant bleeding	Rivaroxaban: 8.1% Standard Tx: 8.1%	Rivaroxaban: 10.3% Standard Tx: 11.4%	Apixaban: 4.3% Standard Tx: 9.7%	Dabigatran: 5.6% Standard Tx: 8.8%	Dabigatran: 5.0% Standard Tx: 7.9%	Edoxaban: 8.5% Standard Tx: 10.3%

CrCL = creatinine clearance; DVT = deep vein thrombosis; INR = international normalized ratio; PE = pulmonary embolism; TTR = time in therapeutic range; Tx = treatment.

* Standard therapy is defined as the use of short-acting anticoagulant agent (ie, intravenous heparin, low-molecular-weight heparin) followed by a vitamin K antagonist.

[†] TTR for vitamin K antagonism.

[‡] Symptomatic VTE and VTE-related death.

[§] Major bleeding is defined per the International Society of Thrombosis and Haemostasis guidelines.

^{||} Clinically relevant bleeding is defined as the composite of major and clinically relevant nonmajor bleeding per the International Society of Thrombosis and Haemostasis guidelines.

[€] Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy.

group. Furthermore, a subgroup analysis in patients with frailty, malignancy, and large thrombus burden as well as a history of recurrent VTE revealed similar efficacy and safety profiles.

Apixaban

The Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy (AMPLIFY) trial was a randomized, double-blind study comparing apixaban (10 mg twice daily for the first 7 days followed by 5 mg twice daily) to standard therapy (low-molecular-weight heparin followed by warfarin) for 6 months in patients with a proximal deep vein thrombosis and/or pulmonary embolism.⁸ The primary efficacy end point was the composite of symptomatic recurrent VTE or VTE-related death, whereas the main safety outcome was major bleeding. Notably, patients with a provoked VTE without the existence of a persistent risk factor and patients with cancer whose treatment plan included 6 months or more of low-molecular-weight heparin were excluded. Patients who underwent neurosurgery or experienced an ischemic stroke within a week of randomization; experienced head trauma or major surgery within 2 months; or experienced intracranial, intraocular, or gastrointestinal bleeding within 6 months were deemed ineligible. As in the Einstein trials, patients undergoing a thrombectomy, insertion of a caval filter, or exposure to a fibrinolytic agent were excluded. Patients with active liver disease or reduced renal function (creatinine clearance < 25 mL/min) were also not

allowed to participate in the study. The use of dual antiplatelet therapy or potent inhibitors of the cytochrome P450 system was prohibited. Apixaban was found to be as effective as standard therapy with significantly less major bleeding. There were also no differences in the rate of permanent drug discontinuation between the treatment arms. Thirty-six percent to 38% of patients with a PE were considered to have extensive thrombus burden.

Dabigatran

The RE-COVER study was a randomized, double-blind, non-inferiority trial comparing dabigatran 150 mg twice daily with warfarin.⁹ Unlike the aforementioned studies, patients were treated with a parental anticoagulant for a median of 9 days before starting dabigatran. Patients with a PE associated with hemodynamic instability or requiring thrombolytic therapy, recent unstable cardiovascular disease, abnormal liver function, and/or creatinine clearance < 30 mL/min were excluded. Patients taking up to 100 mg acetylsalicylic acid were allowed to participate. The primary efficacy outcome was defined as the composite of symptomatic VTE or VTE-associated death in the 6 months after randomization. Several safety outcomes were investigated, including bleeding events, acute coronary syndrome, other adverse events, and results of hepatic function tests. Dabigatran was found to be as effective and safe as standard therapy in reducing recurrent VTE. There was a trend toward more gastrointestinal hemorrhage in patients treated with dabigatran. More

patients treated with dabigatran stopped therapy due an adverse event ($P = 0.05$) and dyspepsia was more common in the dabigatran group ($P < 0.001$). There were no major differences in the rates of acute coronary events or abnormal liver function tests between the groups. The RE-COVER II study had a similar design and study end points to the original RE-COVER trial. As in the original study, there was no difference between dabigatran and warfarin in the composite of symptomatic VTE or VTE-related death. Major bleeding occurred equally in both groups, whereas dabigatran was associated with a statistically significant decrease in the composite of major or clinically relevant nonmajor bleeding compared with vitamin K antagonism. A pooled analysis of the RE-COVER trial results was also undertaken that showed no difference in recurrent VTE or major bleeding between dabigatran or warfarin. However, dabigatran was associated with significantly less major or clinically relevant nonmajor bleeding. Furthermore, there were numerically more acute coronary syndromes in patients treated with dabigatran, but this did not reach statistical significance.¹⁰

Edoxaban

The Hokusai-VTE trial was a randomized, double-blind, non-inferiority study comparing the effects of edoxaban 60 mg once daily (or 30 mg once daily in patients with a creatinine clearance 30–50 mL/min or a body weight < 60 kg) with warfarin in patients with an acute VTE.¹¹ The principal efficacy outcome was the incidence of symptomatic, recurrent VTE, whereas the principal safety measure was the composite of major or clinically relevant nonmajor bleeding (clinically relevant hemorrhage). Forty percent of patients were diagnosed with a PE (with or without a DVT). As in the RE-COVER trials, patients were treated with a standard anticoagulant for at least 5 days before being exposed to the study drug. A median time of 7 days elapsed before the patients assigned to the edoxaban group received the oral, anti-Xa inhibitor. Edoxaban was found to be noninferior to warfarin in preventing the primary efficacy outcome, whereas it was superior to vitamin K antagonism in reducing the risk of clinically relevant bleeding (Table 2).

Clinical Trial Results for Extended Treatment of VTE

Rivaroxaban

The Einstein Extension trial was a double-blind trial in which patients with either a DVT or PE who were treated for at least 6 months with either standard therapy or rivaroxaban were randomly assigned to continue treatment with rivaroxaban 20 mg daily or placebo.⁵ The exclusion criteria were the same as in the Einstein acute DVT trial. The majority of patients were treated for at least 6 months. The primary efficacy outcome was symptomatic, recurrent VTE and the main safety measure was major bleeding (as opposed to the Einstein DVT and PE trials, which investigated the composite of major and clinically relevant non-major bleeding as the main safety outcome). Rivaroxaban reduced the rate of recurrent VTE by 82% ($P < 0.001$ for superiority) with a nonsignificant increase in major bleeding. However, more patients exposed to rivaroxaban experienced the composite of major or clinically relevant nonmajor bleeding ($P < 0.001$). There were no major differences in premature discontinuation of drug, vascular events, or changes in liver function between study drug and placebo.

Apixaban

In the Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment (AMPLIFY-Extension) trial, 2 doses of apixaban (2.5 mg and 5 mg, twice daily) were compared with placebo in patients who completed at least 6 months of anticoagulation for either a DVT or PE.¹² The main efficacy outcome was defined as the composite of symptomatic recurrent VTE or death from any cause, whereas the primary safety measure was major bleeding. The exclusion criteria were similar to those of the AMPLIFY study. However, patients with thrombophilia, multiple episodes of unprovoked DVT or PE, or those taking potent P-glycoprotein inhibitors were excluded from the extended treatment trial. Both doses of apixaban were found to be superior to placebo in reducing the main efficacy outcome. The rates of major bleeding as well as the composite of major or clinically relevant nonmajor bleeding were not statistically different.

Dabigatran

Two double-blind studies compared dabigatran 150 mg twice daily with either warfarin (RE-MEDY, active-control) or placebo (RE-SONATE, placebo-control) in patients who completed at least 3 months of treatment for VTE with an approved anticoagulant or dabigatran in the RE-COVER trials.¹³ Participants in the active-control study were treated for an average of 15.8 months, whereas those enrolled in the placebo-control study were treated for approximately 5.5 months on average. Patients considered to have an increased risk of a recurrent VTE were enrolled in the RE-MEDY study. The primary efficacy outcome was symptomatic, recurrent VTE in both trials. Unexplained death was also included in the primary efficacy outcome in the placebo-control study. Thrombolytic therapy within 14 days before enrollment and patients with inferior vena cava filters were not permitted to participate in the active-control study. Patients with a malignancy were excluded from the RE-SONATE trial.

Dabigatran was found to be as effective as warfarin and superior to placebo for the efficacy outcomes. However, numerically more patients experienced recurrent VTE in the active-control study and the upper limit of the confidence interval for the hazard ratio approached the prespecified noninferiority margin, which was criticized as being too large. There was a trend toward less major bleeding with the direct thrombin inhibitor compared with warfarin; however, significantly fewer patients treated with dabigatran experienced the composite of major or clinically relevant bleeding events. Compared with placebo, significantly more clinically relevant bleeding events occurred in patients exposed to dabigatran with no significant difference in major bleeding observed between these 2 groups. Acute coronary syndrome occurred more frequently in those patients exposed to direct thrombin inhibition in the active-control study ($P = 0.02$). However, statistically more patients treated with dabigatran had coronary artery disease compared with those treated with warfarin (8.4% vs 6.1%, respectively). There was no difference in acute coronary syndrome between recipients of dabigatran and placebo. Unlike the RE-COVER study, there was no difference in the rate of drug discontinuation in patients exposed to dabigatran in both the active-control and placebo-control studies.

Choosing the Ideal Anticoagulant

Although rivaroxaban and dabigatran are the only new oral anticoagulants approved for the treatment of VTE, the therapeutic

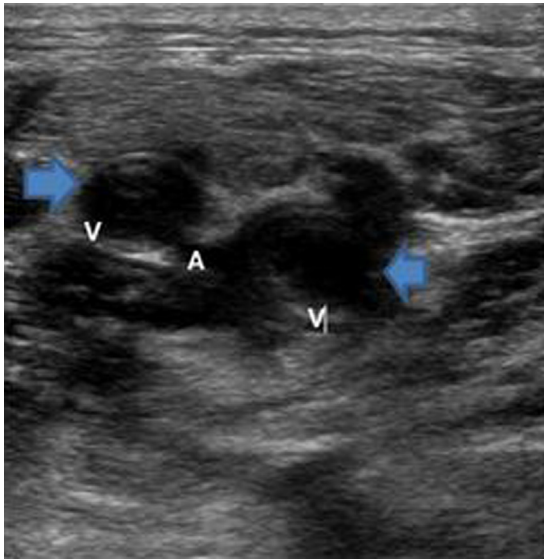


Figure 1. Ultrasound image of calf veins with compression. Blue arrows indicate dilated veins that do not compress, indicating the presence of a deep vein thrombosis.

armament is likely to increase in the future based on the results of the aforementioned trials. Furthermore, all of the anticoagulant agents discussed in this article (with the exception of edoxaban) are approved for the prevention of stroke in patients in nonvalvular atrial fibrillation. Clinicians will thus need to choose among these options. Although no trial has directly compared these new medications with one another, some of these agents may be more preferable for certain patient populations based on their pharmacologic profiles and results of the individual trials. The following cases highlight the potential advantages and disadvantages of the new oral anticoagulants with respect to each other and conventional therapy in specific patient groups.

Case #1

A 52-year old man underwent an uneventful arthroscopic repair of a torn right medial meniscus injury 1 month prior. He presented with a chief complaint of right calf pain and swelling that began within the past 48 hours. He takes no medications and has no other medical conditions. On examination, he weighs 77 kg and his vital signs are normal. He has 1+ right lower extremity pitting edema extending from the ankle to the upper calf medially along with calf tenderness on palpation. A lower extremity venous Doppler ultrasound was performed and is shown in [Figure 1](#). He also underwent a laboratory assessment approximately 1 month ago that revealed a creatinine clearance of 125 mL/min as calculated by the Cockcroft-Gault formula along with a normal blood count and liver function panel.

Discussion

As shown in [Figure 1](#), both of the patient's gastrocnemius veins were dilated and noncompressible, consistent with a DVT in these vessels without extension into the more proximal veins (ie, isolated calf vein thrombosis [ICVT]). Patients with an ICVT were not studied in the aforementioned clinical trials and there is a lack of large-scale and well-designed clinical trials to address the question of whether or not full dose anticoagulation is necessary in these patients. Given the likely similar pathogenesis and risk factors for an ICVT and proximal DVT, the results of the trials investigating the novel anticoagulants can likely be extrapolated to the patient population

with an ICVT. The American College of Chest Physicians guideline suggests treating patients with an ICVT with full-dose anticoagulation if they are symptomatic and/or have risk factors for thrombus propagation (such as immobility or an active malignancy).¹⁴ Given our patient's symptoms and a relative reduction in his mobility from his baseline, a decision was made to initiate full-dose anticoagulation therapy after conferring with his orthopedic surgeon. As of now, only rivaroxaban and dabigatran are approved for the treatment of an acute VTE. However, all of the new oral anticoagulants would likely be appropriate for this patient given his young age, lack of comorbidities, normal renal function, and results of the aforementioned trials. However, dabigatran as well as edoxaban were not used as initial therapy in their respective trials because patients were treated with a standard, parental anticoagulant for at least 5 days before being exposed to these medications. On the other hand, apixaban and rivaroxaban were studied for the initial treatment of VTE without the need to wait for at least 5 days before they were used. This difference in study design is reflected in the Food and Drug Administration stipulation that a parental anticoagulant be used for 5 to 10 days before starting dabigatran for the treatment of an acute VTE. Thus, in addition to the conventional anticoagulants, the other options for the treatment of this patient is dabigatran 150 mg PO BID (after treating the patient with low-molecular-weight heparin for 5-10 days as an outpatient) or rivaroxaban 15 mg twice daily for the first 3 weeks and then 20 mg daily thereafter.

If, however, the same patient had a creatinine clearance of 40 mL/min, the risk/benefit profile may be different among the new oral anticoagulants. As shown in [Table 1](#), all of these medications are renally excreted but to a different extent. Apixaban appears to be associated with the least amount of renal excretion. There were no differences in the efficacy outcomes in the subgroup analysis according to renal function of the new oral anticoagulants for the treatment of VTE. A subgroup analysis for the safety outcomes in patients with renal impairment was not provided for the RE-COVER and RE-COVER II studies. Although there were no differences in the bleeding outcomes in the subgroup analysis according to renal function for the other anticoagulants, the medications with the least amount of renal excretion, such as apixaban or rivaroxaban, may be better options in patients with mild renal insufficiency given their pharmacologic profile. A recently published meta-regression analysis of the VTE and atrial fibrillation clinical trials revealed a

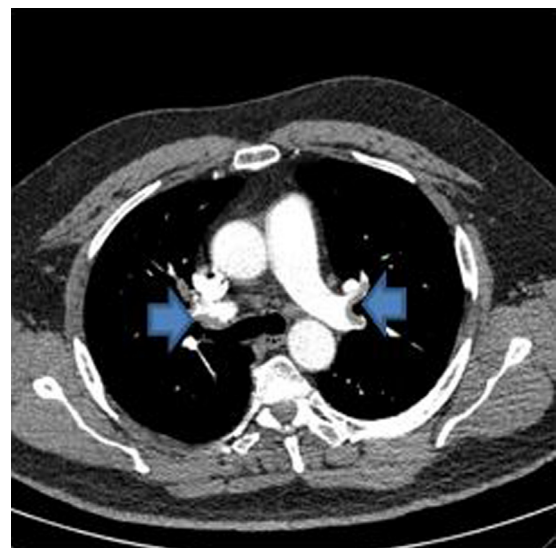


Figure 2. Chest computed tomography image. Blue arrows indicate filling defects consistent with the presence of pulmonary embolism.

reduced risk of major bleeding in patients with moderate to severe renal impairment who were treated with apixaban or rivaroxaban.¹⁵ All patients with active liver disease were excluded from the aforementioned trials. However, dabigatran is the only new anticoagulant that does not interact with the cytochrome P450 system. This medication may thus be preferred over the others in patients taking medications that have extensive hepatic metabolism or those who may be exposed to such medications in the future, such as the HIV population and those with a seizure disorder.

Case #2

A 62-year old man with a history of an unprovoked left popliteal vein DVT 2 years ago presented with a chief complaint of a 1-week history of dyspnea on exertion. His comorbidities include diabetes mellitus (type 2), hypertension, and hyperlipidemia. He takes full-dose aspirin, metformin, diovan, and insulin. On examination, his vital signs are normal and he has 1+ left leg pitting edema with hemosiderin deposition distally on his anterior shin. Otherwise, his examination is unremarkable. His laboratory analysis is normal with the exception of a minimally elevated troponin T level (0.04 ng/mL with an upper limit of normal of 0.01 ng/mL). A computed tomography angiogram of the chest was ordered and the images are shown in Figure 2. An echocardiogram revealed normal right ventricular function.

Discussion

The patient was diagnosed with extensive bilateral PE. Due to his elevation in troponin T level, his PE would be classified as submassive given his normal hemodynamics. All of the new anticoagulants have been studied in patients with PE. However, exclusion criteria for all studies were the presence of hemodynamic instability and the use of thrombolysis. Patients treated with inferior vena cava filters were also excluded in the AMPLIFY, Einstein, and Hokusai-VTE trials; however, thrombus burden was described in these 3 studies but not in RE-COVER. Although inconsistent, there is evidence that an abnormal vascular obstruction index, which is a reflection of the extent of thrombosis of the vasculature, is associated with worse outcomes in patients with a PE.^{16–19} Approximately one-quarter of patients in the Einstein-PE trial were considered to have extensive thrombus burden based on the anatomic distribution of filling defects. The first 400 patients in this trial were also screened for asymptomatic deterioration by undergoing mandatory imaging after the first 3 weeks of therapy. Apixaban was also used in approximately one-third of patients who were categorized as having an extensive thrombus burden.

Certain markers associated with right ventricular dysfunction, such as an abnormal echocardiogram, computed tomography scan, troponin or pro-B-type natriuretic peptide values, have been associated with poorer outcomes in patients with a PE.²⁰ Unlike the apixaban and rivaroxaban studies, the Hokusai-VTE study also published a subgroup analysis of its patients with a PE and evidence of right ventricular strain as determined by an elevated pro-B-type natriuretic peptide or a relative increase in the size of the right ventricle compared with the left. In this subgroup of participants, which accounted for approximately 30% of the study population, fewer patients treated with edoxaban experienced the primary efficacy outcome compared with warfarin (3.3% vs 6.2%, 95% confidence interval, 0.28–0.98). Unless more evidence surfaces for the other anticoagulants, edoxaban, if approved, may be a more appealing option in patients with a submassive PE. However, as discussed above, a parental anticoagulant will likely need to be used for the first 5 to 10 days of treatment before patients begin edoxaban.

Dabigatran, rivaroxaban, and apixaban have also been studied in patients with acute coronary syndrome. However, all

3 medications were associated with an increase in major or clinically significant bleeding when combined with antiplatelet therapy in these trials.^{21–23} Dual antiplatelet therapy (with dose limitations) was permitted in the Einstein trials, whereas aspirin monotherapy (with dose limitations) was allowed in the AMPLIFY, AMPLIFY-Ext, Hokusai-VTE, and RE-COVER trials. The use of antiplatelet medications in the RE-MEDY and RE-SONATE studies was not specified. With the exception of AMPLIFY-Ext and Hokusai-VTE studies, in which 12% to 14% and 9% of patients were exposed to aspirin, respectively, the percentage of patients also taking antiplatelet medications in the VTE trials was not specified. Furthermore, the Hokusai-VTE trial was the only study that provided a subgroup analysis for the safety outcomes according to the use of antiplatelet therapy (which found no difference between edoxaban and warfarin for major and clinically relevant nonmajor bleeding). Based on the results of the acute coronary syndrome trials (even though a different patient population was studied) and historical data, which have shown an increase in major bleeding when standard anticoagulation therapy was used with antiplatelet medications, the new oral anticoagulants should be used cautiously with antiplatelet drugs.

Dabigatran was associated with a higher rate of acute coronary events compared with warfarin in the atrial fibrillation study (RE-LY).²⁴ This finding was also seen in the extended treatment study RE-MEDY (active-control) but not in RE-SONATE (placebo-control) or the acute VTE study (RE-COVER). A meta-analysis of several trials that compared this direct thrombin inhibitor with different therapies, including placebo, found an increased risk of acute coronary syndrome with dabigatran.²⁵ The anti-Xa inhibitors may thus be more preferable over dabigatran in patients with coronary artery disease. In all of the atrial fibrillation studies, the reduction in stroke seen with the new oral anticoagulants was primarily driven by a reduction in intracranial hemorrhage. However, dabigatran 150 mg twice daily was the only medication that also significantly reduced the risk of ischemic stroke.^{24,26,27} Dabigatran may thus be preferable in this patient population.

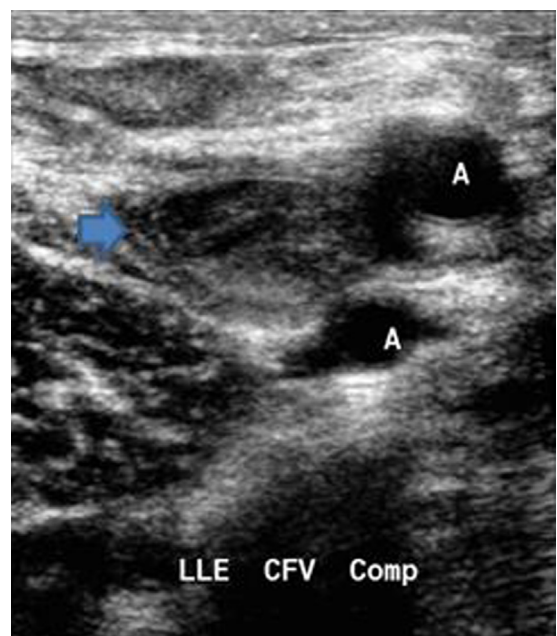


Figure 3. Ultrasound image of common femoral vein with compression. Blue arrow indicates a dilated and noncompressible vein with echogenic material consistent with deep vein thrombosis.

Table 3Clinical trials investigating the new oral anticoagulant agents for the extended treatment of venous thromboembolism (VTE)^a

Variable	Einstein-Ext	AMPLIFY-Ext ^e	RE-MEDY	RE-SONATE
Trial design	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized	Double-blind, randomized
Regimen	Rivaroxaban 20 mg daily vs placebo	Apixaban 2.5 mg or 5 mg BID vs placebo	Dabigatran 150 mg BID vs warfarin	Dabigatran 150 mg BID vs placebo
Average age (y)	58	56–57	54–55	56
Index event [†] (%)	DVT: 60–64 PE: 36–40	DVT: 65–67 PE: 34–35	DVT: 65–66 PE: 34–35	DVT: 63–67 PE: 32
Unprovoked VTE (%)	73–74	91–93	Undefined	Undefined
Prior VTE (%)	14–18	12–15	52–55	2 patients
Malignancy (%)	4–5	Excluded (3–4)	4	Excluded
Thrombophilia (%)	8	Excluded (1–2)	18	10–13
TTR for INR [‡] (%)	—	—	65.3	—
Efficacy outcome [§]	Rivaroxaban: 1.3% Placebo: 7.1%	Apixaban 2.5 mg: 3.8% Apixaban 5 mg: 4.2% Placebo: 11.6%	Dabigatran: 1.8% Warfarin: 1.3%	Dabigatran: 0.4% Placebo: 0%
Major bleeding [¶]	Rivaroxaban: 0.7% Placebo: 0%	Apixaban 2.5 mg: 0.2% Apixaban 5 mg: 0.1% Placebo: 0.5%	Dabigatran: 0.9% Warfarin: 1.8%	Dabigatran: 0.3% Placebo: 0%
Clinically relevant bleeding [¶]	Rivaroxaban: 6.0% Placebo: 1.2%	Apixaban 2.5 mg: 3.2% Apixaban 5 mg: 4.3% Placebo: 2.7%	Dabigatran: 5.6% Warfarin: 10.2%	Dabigatran: 5.3% Placebo: 1.8%

DVT = deep venous thrombosis; INR = international normalized ratio; PE = pulmonary embolism; TTR = time in therapeutic range.

^a Patients were treated with either a standard anticoagulant agent or study drug for at least 3 mo before being randomized into the extended treatment trials.[†] DVT refers to DVT only, whereas PE could be PE with or without DVT.[‡] TTR for vitamin K antagonism.[§] Symptomatic VTE and VTE-related death.[¶] Major bleeding is defined per the International Society of Thrombosis and Haemostasis guidelines.[¶] Clinically relevant bleeding is defined as the composite of major and clinically relevant nonmajor bleeding per the International Society of Thrombosis and Haemostasis guidelines.^e Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy—Extended Treatment.

Case #3

A 45-year old man with a medical history significant for Crohn's disease presented with a 1-week history of left leg swelling. He also had an unprovoked left femoral-popliteal vein thrombosis 15 years ago for which he received a 6-month duration course of warfarin. He underwent a partial small bowel resection 1 month prior for intractable abdominal pain. His medications are intravenous hydrocortisone and mesalamine. His examination is significant for 2+ left pitting edema in the pretibial region. His laboratory workup is notable for a hemoglobin level of 6.7 g/dL. The venous Doppler ultrasound of his left leg is shown in [Figure 3](#). Intravenous heparin was initiated and the primary medical service inquired about the use of the new oral anticoagulants.

Discussion

The patient is diagnosed with DVT of the common femoral vein extending into his popliteal vein. His severe anemia was considered to be due to his active Crohn's disease and recent surgery. The use of the new oral anticoagulants would likely be considered inappropriate for this patient. Although all of these medications have short half-lives, they do not have an antidote and the reversal of their anticoagulant effects has not been extensively studied. The patient was unable to tolerate any food intake; thus, warfarin should also likely be avoided. Low-molecular-weight heparin likely best balances the risk/benefit profile for this patient given its short half-life and partial reversibility.

Significantly more patients who were exposed to dabigatran experienced a gastrointestinal hemorrhage in the atrial fibrillation study (RE-LY) and there was a trend for more gastrointestinal hemorrhage in the RE-COVER trial.^{9,24} Rivaroxaban was also associated with a significantly higher rate of gastrointestinal bleeding events compared with warfarin in its atrial fibrillation study.²⁷ A recent meta-analysis of the clinical trials in the atrial

fibrillation population confirmed a significantly increased risk of gastrointestinal hemorrhage with the novel anticoagulants compared with vitamin K antagonism.²⁸ However, apixaban was not associated with this bleeding outcome in either the VTE or atrial fibrillation studies.²⁶ This medication may thus be more appropriate in patients who have experienced a gastrointestinal hemorrhage or who are at risk for this complication. Dyspepsia was significantly more common in patients taking dabigatran in the RE-LY and RE-COVER studies. Patients who may be predisposed to his complication, such as those with irritable or inflammatory bowel disease, peptic ulcer disease, or gastritis, may better tolerate the anti-Xa inhibitors.

As noted in [Tables 2 and 3](#), few patients with a malignancy or hypercoagulable conditions were studied in the VTE trials. These agents should thus be used cautiously in patients with active cancer. However, dabigatran was investigated in 18% of patients with thrombophilia in the extended treatment study and this may be a feasible option for the extended treatment of VTE in this patient population. Certain coagulation assays, including those testing for activated protein C resistance, lupus anticoagulants, and protein functional deficiencies may be falsely abnormal in patients taking the new oral anticoagulants.³

Conclusions

Until recently, the therapeutic options for the treatment of DVT and PE have been limited. The approval of rivaroxaban and dabigatran for the treatment of VTE, and the likely approval of other anticoagulants, represents a paradigm shift in the treatment of this potentially fatal condition. Although these medications offer potential advantages over conventional therapy, careful postmarketing surveillance will be required to establish their efficacy and safety in larger and more specific patient populations. Elderly patients were underrepresented in all of the VTE trials—the average age of patients studied for all of the trials was in the

middle 50s. Although a recent, pooled analysis of the rivaroxaban VTE trials did not show a difference in efficacy or safety in patients older than age 75 years, the effects of the new anticoagulants in the elderly population, particularly outside of the setting of a clinical trial, is not well established. Patients with multiple comorbidities also appear to be underrepresented in these trials and may be better suited to treatment with standard anticoagulation. Noncompliant patients should not be prescribed the new anticoagulant agents because of their short half-lives. As described above, the efficacy and safety of these new medications has not been well established in patients with an active malignancy. Despite a lack of head-to-head comparison trials, some of the new oral anticoagulants may be better suited than others for certain patient populations based on their pharmacologic profiles and results of individual studies. Careful assessment of the risks and benefits of these new medications will remain essential in ensuring that these drugs are implemented appropriately into daily clinical practice.

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Conflicts of Interest

Dr Merli has received grant/research support from BMS, Johnson & Johnson, and Sanofi-Aventis; has performed scientific consultation duties for BMS, Johnson & Johnson, and Sanofi-Aventis, and received research support from Portola Pharmaceuticals Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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