Perioperative venous thromboembolic disease and the emerging role of the novel oral anticoagulants: An analysis of the implications for perioperative management

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ABSTRACT

Venous thromboembolism includes 2 inter-related conditions: Deep venous thrombosis and pulmonary embolism. Heparin and low-molecular-weight heparin followed by oral anticoagulation with vitamin K agonists is the first line and current accepted standard therapy with good efficacy. However, this therapeutic strategy has many limitations including the significant risk of bleeding and drug, food and disease interactions that require frequent monitoring. Dabigatran, rivaroxaban, apixaban, and edoxaban are the novel oral anticoagulants that are available for use in stroke prevention in atrial fibrillation and for the treatment and prevention of venous thromboembolism (HYPERLINK\l "1). Recent prospective randomized trials comparing the NOACs with warfarin have shown similar efficacy between the treatment strategies but fewer bleeding episodes with the NOACs. This paper presents an evidence-based review describing the efficacy and safety of the new anticoagulants compared to warfarin.

INTRODUCTION

Venous thromboembolism (VTE) is a relatively common disease.[1] Several hundred thousand patients are diagnosed with VTE in the United States (US) with an annual mortality rate between 5% and 12%.[2] Death is usually due to large pulmonary emboli and frequently occurs when the condition is undiagnosed or if there is a delay in the diagnosis. Death occurs within the first few weeks of the diagnosis being made.[2]

VTE is considered a chronic disease in the majority of patients, because of the tendency for recurrence. The conventional treatment of VTE is with an initial course of parenteral rapid-onset anticoagulant, followed by 3–6 months of an oral Vitamin K antagonist (VKA).[3] This treatment has an efficacy rate >90%; however, this

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success is offset by the risk of bleeding. In patients who are at risk for recurrent disease, treatment can be extended beyond 6 months or lifelong in selected clinical circumstances.

Recent trials on novel oral anticoagulants (NOACs) use an initial period of unfractionated or fractionated heparin, except for the rivaroxaban and the apixaban studies, where these agents were initiated without the use of a parenteral agent. This omission of parenteral anticoagulation presents a dramatic paradigm shift in VTE management. These studies also demonstrate that the NOACs are safer and effective than that of the conventional treatment of VTE using heparin and VKAs.[4-7]

THE NOVEL ANTICOAGULANT CLASS OF DRUGS

There are four novel anticoagulants that are currently available worldwide [Table 1]. Each has unique pharmacokinetics and food and drug interactions via the cytochrome system. Each exhibits variable absorption and predominantly hepatic or renal excretion. Knowledge of these pharmacodynamic properties is key to the understanding and safe use of the NOACs to reap the greatest benefit while minimizing harm.

The first is dabigatran that is the only oral direct thrombin inhibitor (DTI) of the group; it affects bound and unbound thrombin. It has predominant renal clearance and is dosed twice daily. In the US, there are 2 dose ranges such as 150 mg twice a day and 75 mg twice a day. The rest of the world has 150 mg twice a day and

110 mg twice a day.[8] The remaining 3 agents are factor Xa inhibitors. Rivaroxaban is the first of the group to be studied, achieving approval for use in stroke prevention in atrial fibrillation as well as for the management of VTE.[6,9] Rivaroxaban has modest renal clearance; the remainder is through hepatic clearance [Table 1] and is dosed once a day. The second factor Xa inhibitor is apixaban that has a slightly lower renal clearance but also has hepatic clearance and is dosed at twice a day [Table 1]. The third drug in this class is edoxaban, which has modest renal clearance and is dosed once daily. The Xa inhibitors affect factor Xa, which is important for the intrinsic and extrinsic pathways of the coagulation cascade [Figure 1 and Table 2].

Knowledge of the pharmacodynamic characteristics of these novel anticoagulants has important implications in clinical practice. Renal elimination and drug half-life, which are discussed with the description of each medication, are also important for both dosing as well as for timing interruption for planned surgical procedures and perioperative management of the NOACs. Most of the novel anticoagulants have a wide therapeutic range, in contradistinction to warfarin. The Xa inhibitors have interactions with medications that affect the CYP3A4 and beta glycoprotein (P-gP) [Table 3].[10]

NOVEL ANTICOAGULANTS COMPARED TO WARFARIN IN RANDOMIZED CLINICAL TRIALS

This section reviews the pharmacology and the pertinent findings from the randomized clinical trials that led to the approval of the NOAC for the use in the prevention

Table 1: The second factor Xa inhibitor is apixaban that has a slightly lower renal clearance but also has hepatic clearance, and is dosed at twice a day

Drug	Mechanism	Dose and Frequency	Hours to Cmax	Half-Life, Hours	Renal Elimination, %
Dabigatran	IIa (thrombin)	110, 150 mg BID	2-4.5	12-14	80
Rivaroxaban	Xa	20 (15) mg OD	1-3	9-13	33
Apixaban	Xa	5 (2.5) mg BID	1-2	8-15	25
Edoxaban	Xa	30, 60 mg OD	–	8-10	35
Warfarin	Synthesis of II, VII, IX, X	Variable OD	72-96	40	<1

or treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE) and the strategy for treatment considerations when using these drugs as well as the efficacy and risks.

Warfarin

Warfarin acts by antagonizing Vitamin K that serves as a co-factor in the gamma carboxylation of coagulation factors II, VII, IX, and X, as well as protein C and S. It requires 36–48 h to onset of action. The initial dose required for prophylaxis and treatment of venous thrombosis or PE is 2–5 mg p.o. daily for 2 days or 10 mg p.o. for 2 days in healthy individuals. A typical maintenance dose ranges between 2 and 10 mg/day. Patients respond variably to initial dosing since many factors affect the pharmacokinetics.

Figure 1: The Xa inhibitors affect factor Xa, which is important for the intrinsic and extrinsic pathways of the coagulation cascade

Both genetic and environmental factors may influence individual response to warfarin. Warfarin works by inhibiting Vitamin K epoxide reductase complex subunit 1, an enzyme that reduces Vitamin K epoxide to its active form.[11] Mutations in the gene encoding this enzyme may be responsible for hypersensitivity to warfarin.

The bleeding risk associated with warfarin therapy limits its role as an ideal anticoagulant. Furthermore, the need for frequent international normalized ratio (INR) testing, multiple dose adjustments to reach therapeutic range, and the multiple drug and food interactions of this medication made it challenging to use. Hence, many alternative anticoagulants have been developed to overcome these limitations.
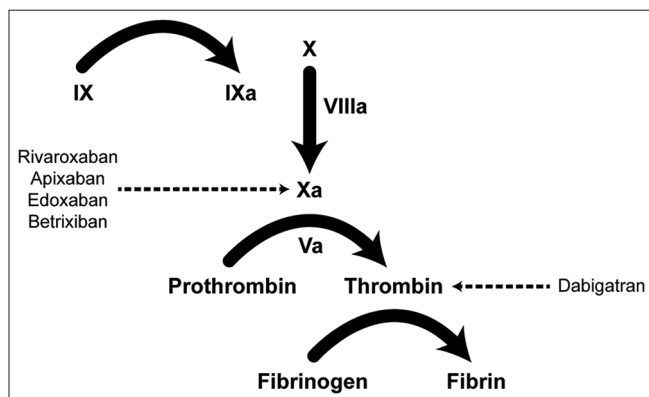
Dabigatran (Pradaxa: Boehringer Ingelheim Pharmaceuticals, Inc., Richfield, CT, USA)

Dabigatran is an oral anticoagulant from a class of DTIs.[12] DTIs act by directly inhibiting the enzyme thrombin (factor II), both the free and the clot-bound forms, as well as thrombin-induced platelet aggregation. This medication was approved by the Food and Drug Administration (FDA) in 2014 for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days. Dabigatran is also approved for use to reduce the risk for developing DVT and to reduce the risk for PE recurrence in patients who have been previously treated for these conditions using the conventional VKA.

Table 2: The Xa inhibitors affect factor Xa

Drug	Indication					
	DVT Treatment	PE Treatment	VTE Prophylaxis	ACS with DAT	Atrial Fibrillation	Mechanical Valves
Dabigatran	Yes*	Yes*	No	No	Yes	No
Rivaroxaban	Yes†	Yes†	Yes	Yes in EU‡ No in USA	Yes	No
Apixaban	Yes†	Yes†	Yes	No	Yes	No
Edoxaban	Yes	Yes	Yes in Japan only	No	Yes	No

*After 5-10 of parenteral anticoagulation therapy
†Without prior parenteral anticoagulation therapy
‡Combined with aspirin with or without clopidogrel or ticlopidine, but not with other DAPT regimens
ACS, acute coronary syndrome; DAT, dual antiplatelets therapy

Table 3: The Xa inhibitors have interactions with medications that affect the CYP3A4 and beta glycoprotein

General Recommendations All NOACs (Apixaban, Dabigatran, Edoxaban, Rivaroxaban)	
Avoid use with	**Drugs that increase the risk of bleeding** • Anticoagulants (argatroban, bivalirudin, enoxaparin, fondaparinux, heparin, warfarin) **Drugs that decrease the anticoagulant effect** • Carbamazepine, dexamethasone, phenobarbital, phenytoin, primidone, rifampin, St. John's Wort **Drugs that increase the anticoagulant effect** • Azole antifungals, grapefruit juice, HIV protease inhibitors, urokinase (systemic), vorapaxar
Dose reduce or use extreme caution with	**Drugs that may increase the anticoagulant effect** • Amiodarone, carvedilol, clarithromycin, cyclosporine (systemic), dipyridamole, dronedarone, erythromycin (systemic), nicardipine, propranolol, quinidine, quinine, ranolazine, reserpine, tacrolimus (systemic), tamoxifen, tyrosine kinase inhibitors, verapamil **Drugs that may decrease the anticoagulant effect** • Estrogen, progestins
Use caution with	**Drugs that may increase the risk of bleeding** • Antiplatelets (abciximab, aspirin, clopidogrel, eptifibatide, prasugrel) • Omega 3 fatty acids, vitamin E • NSAIDS **Drugs that may decrease the anticoagulant effect of *dabigatran* only** • Antacids (H_2 antagonists, proton pump inhibitors), atorvastatin

For more detailed interaction information, please see supplemental appendix

Dabigatran etexilate is a pro-drug that is hydrolyzed to the active form, dabigatran, by carboxylesterases in the bloodstream after its absorption from the intestinal lumen. Dabigatran etexilate is a substrate of the efflux transporter P-gp, which transports dabigatran back into the gastrointestinal tract for excretion. Inducers of P-gp transporter may reduce the bioavailability of dabigatran if they were co-administered. Rifampin, St. John's wort, carbamazepine, tipranavir, and phenytoin are some of the P-gp inducers. Inhibitors of the P-gp transporter will do the opposite; they will increase the bioavailability of dabigatran etexilate and may increase the risk of bleeding. Amiodarone, azoles, and antibiotics such as clarithromycin, cyclosporine, verapamil, diltiazem, quinidine, and protease inhibitors are some of the P-gp transporter inhibitors [Table 3].

Approximately, 80% of dabigatran is excreted unchanged by the kidneys. Thus, we recommend that patients receiving dabigatran be monitored closely when the creatinine clearance (CrCl) is 15–30 ml/min/1.73 m². Dabigatran is contraindicated when the CrCl is <15 ml/min or in the presence of severe hepatic failure and during pregnancy.

Dabigatran does not require routine monitoring under normal conditions. However, under certain circumstances such as intracerebral bleeding or overdose, it may be necessary to perform some coagulation tests to plan for adequate management. Ecarin clotting time and thrombin time determined by hemoclot thrombin inhibitor assay are the most sensitive tests.[13] The activated partial thromboplastin time (aPTT) is widely available, but is less accurate at subtherapeutic dabigatran levels.

There is no specific antidote for dabigatran. Because of the short half-life of dabigatran (12–14 h after multiple doses), cessation of therapy for 2–4 days is sufficient to reverse its action in nonurgent cases.[14] Suggested treatments in case of major bleeding include administration of 4-factor prothrombin complex concentrate (PCC), recombinant activated factor VII, or hemodialysis in patients with kidney failure. Administration of activated charcoal should be recommended if the last dose was within 2 h. A potential dabigatran antidote (idarucizumab) is undergoing clinical studies.[15,16]

Two trials investigated the treatment of VTE with either dabigatran or warfarin. These trials are the dabigatran versus warfarin in the treatment of acute VTE (RE-COVER) trial published in 2009 and the RE-COVER II trial published in 2011.[7,17] Both were double-blinded trials that used dabigatran at a dose of 150 mg b.i.d. RE-COVER included 2539 patients with acute VTE and the treatment of acute VTE with dabigatran or warfarin and pooled analysis (RE-COVER II) trial included 2589 patients with very similar characteristics.[18] The results of the RE-COVER trial show recurrent VTE or fatal PE at 2.4% for the dabigatran group and 2.1% for the warfarin group. The difference in risk was 0.4% points (95% confidence interval [CI] −0.8 to 1.5, *P* < 0.001). For the safety outcome, major bleeding was at 1.6% for the dabigatran group and 1.9% for the warfarin group (hazard ratio with dabigatran for major bleeding was 0.82, 95% CI 0.45–1.48; *P* = 0.38). In the RE-COVER II trial, the recurrent VTE or fatal PE was 2.3% for the dabigatran group and 2.2% for the warfarin group (*P* < 0.001). For major bleeding, there were 15 patients in the dabigatran group and 22 patients in the warfarin group (hazard ratio 0.69, 95% CI 0.36–1.32) [Table 3].

Dabigatran was also studied for the treatment of VTE in patients who were believed to be at increased risk of recurrent disease in the RE-MEDY and the extended use of dabigatran, warfarin, or placebo in VTE (RE-SONATE and RE-MEDY) Trial.[19] The RE-MEDY study design included patients who were already treated for

the acute events and needed to be maintained on anticoagulation therapy. Patients were randomized to dabigatran at 150 mg b.i.d. versus warfarin. Up to 36 months follow-up, there was no difference in the estimated cumulative event rate between the two groups. The RE-SONATE trial was very similar to the RE-MEDY trial; however, the control arm was a placebo. In this group of patients, there was a significant decrease in risk of recurrent VTE in patients treated with dabigatran (hazard ratio 0.08, 95% CI 0.02–0.25, $P < 0.001$). This was associated with a significantly increased risk of bleeding (hazard ratio of major or clinically significant nonmajor bleeding is 2.92, 95% CI 1.2–5.60, $P = 0.001$) [Table 4].

Rivaroxaban (Xarelto Janssen Pharmaceuticals, Titusville, NJ, USA)

Rivaroxaban is a selective direct factor Xa inhibitor. Factor X is the first member of the final common pathway or thrombin pathway. When activated, it works by cleaving prothrombin to thrombin; hence, inhibition of factor Xa affects both the intrinsic and extrinsic pathways of the coagulation cascade. The FDA approved the use of rivaroxaban in 2012 for the treatment of DVT and PE and for the prevention of DVT or PE recurrence after initial treatment. About one-third of rivaroxaban is excreted renally, whereas the remaining two-third is metabolized in the liver by cytochrome P450 enzymes (CYP3A4 and CYP2J2) and P-gp enzymes. Thus, co-administration of rivaroxaban is not recommended if patients are receiving systemic therapy with CYP3A4 or P-gp inhibitors such as antimycotics (azoles) or human immunodeficiency virus protease inhibitors.[20] The advantages of rivaroxaban, as with all NOACs, are the rapid-onset and the short half-life and elimination time when renal function is normal. The time required for rivaroxaban to peak in the plasma after administration is 2–4 h; its half-life is 5–9 h and could reach 11–13 h in an elderly group.[21] Although monitoring of the medication levels is not required, measurement of anti-factor Xa, prothrombin time (PT), and INR is useful in certain circumstances. Possible reversal agents are 4-factor PCC and activated PCC.

Rivaroxaban was tested in the treatment of VTE in the treatment of proximal DVT with the oral direct factor Xa inhibitor rivaroxaban ODIXa-DVT trial that was a Phase II trial mainly for dose and safety outcomes.[22] The doses used in this trial were 10, 20, or 30 mg b.i.d. and 40 mg once a day. There was no significant trend observed in the dose-response relationship between twice daily rivaroxaban and the primary efficacy endpoint ($P = 0.67$)

Table 4: Significantly increased risk of bleeding

Study Population	RECOVER Study N=2,539					RECOVER-2 Study N=2,589					RE-MEDY Study N=2,856					RE-SONATE Study N=1,343				
	Warfarin, %	Daigatran, %	Hazard Ratio	95% CI	P Value	Warfarin, %	Daigatran, %	Hazard Ratio	95% CI	P Value	Warfarin, %	Daigatran, %	Hazard Ratio	95% CI	P Value	Placebo, %	Daigatran, %	Hazard Ratio	95% CI	P Value
	After 5-11 Days of Heparin or LMWH										Completed at Least 3 Initial Months of Therapy									
Recurrent VTE	2.1	2.4	1.10	0.65-1.84	<0.001	2.2	2.3	1.08	0.64-1.8	<0.001	1.3	1.8	1.44	0.78-2.64	0.01	5.6	0.4	0.08	0.02-0.25	<0.001
Major bleeding	1.9	1.6	0.82	0.45-1.48	0.38	1.7	1.2	0.69	0.36-1.32	–	1.8	0.9	0.52	0.27-1.02	0.06	0	0.3	–	1.23-2.68	1
Any bleeding	21.9	16.1	0.71	0.59-0.85	0.001	22.1	15.6	0.67	0.56-0.81	–	26.2	19.4	0.71	0.61-0.83	<0.001	5.9	10.5	1.82	–	0.003
Major or clinically significant non-major bleeding	8.8	5.6	0.63	0.47-0.84	0.002	7.9	5.0	0.62	0.45-0.84	–	10.2	5.6	0.54	0.41-0.71	<0.001	1.8	5.3	2.92	1.52-5.60	0.001

or in the dose-response relationship for rivaroxaban b.i.d. and major bleeding (*P* = 0.39) [Table 5]. The oral rivaroxaban for symptomatic VTE (EINSTEIN DVT) and the oral rivaroxaban for the treatment of symptomatic PE (EINSTEIN PE) [Table 4].[23,24] These trials were open label and tested rivaroxaban at 15 mg b.i.d. for the initial 3 weeks, followed by 20 mg once a day compared to enoxaparin and VKA as the second arm of treatment. The duration of this study was 3, 6, and 12 months and included 3449 patients with acute DVT in the EINSTEIN DVT trial and 4832 patients in the acute PE trial [Table 5].

The results of the EINSTEIN DVT trial showed an incidence of recurrent VTE about 2.1% in the rivaroxaban arm and 3% in the enoxaparin-warfarin arm. Major bleeding that occurred in the rivaroxaban arm was 8.1%, and the VKA was 8.1% (hazard ratio 0.97, 95% CI 0.76–1.22, *P* = 0.77). The Kaplan–Meier curve for the cumulative event rate for primary efficacy outcome shows noninferiority for rivaroxaban compared to enoxaparin-warfarin with the 2 curves separating at 30 days with a hazard ratio of 0.68 (95% CI 0.44–1.04, *P* < 0.001) which gives rivaroxaban, a reasonable noninferiority margin, but unfortunately does not meet the superiority margin. The Kaplan–Meier curve for the cumulative event rate for the principal safety outcome that included clinically significant bleeding showed rivaroxaban to be safer when compared to the conventional arm. This led to the conclusion that rivaroxaban offered a simpler strategy to treatment when compared to enoxaparin-warfarin for the treatment of venous thrombosis with good efficacy and an improved safety profile [Table 5].

In the PE trial, the recurrent VTE rate was 2.1% for the rivaroxaban and 1.8% in the enoxaparin/VKA arm. Major bleeding was 10.3% for rivaroxaban and 11.4% enoxaparin/VKA. The Kaplan–Meier curve for the cumulative event rates for the primary efficacy outcome for rivaroxaban was identical to the curve for conventional therapy. It showed that there is no difference between these two treatments. When reviewing the Kaplan–Meier curve for the cumulative event rates for clinically significant bleeding, rivaroxaban appeared to be safer when compared to conventional therapy. When you look at major bleeding, there was quite a difference between rivaroxaban and standard therapy that led to the conclusion that a fixed dose of rivaroxaban alone was a reasonable alternative to conventional therapy and may improve the benefit-risk profile.

Table 5: Enoxaparin-warfarin for the treatment of venous thrombosis

Study Population	EINSTEIN DVT Study N=3,449					EINSTEIN PE Study N=4,832					Einstein-Extension Study N=1,196				
	Rivaroxaban, %	Enoxaparin/ Warfarin, %	Hazard Ratio	95% CI	P Value	Rivaroxaban, %	Enoxaparin/ Warfarin, %	Hazard Ratio	95% CI	P Value	Rivaroxaban, %	Placebo, %	Hazard Ratio	95% CI	P Value
Symptomatic recurrent VTE	2.1	3.0	0.68	0.44-1.04	<0.001	2.1	1.8	1.12	0.75-1.68	0.003	1.3	7.1	0.18	0.09-0.39	<0.001
First major or clinically relevant non- major bleeding	8.1	8.1	0.97	0.76-1.22	0.77	10.3	11.4	0.90	0.76-1.07	0.23	6.0	1.2	5.19	2.3-11.7	<0.001
Major bleeding	0.8	1.2	0.65	0.33-1.30	0.21	1.1	2.2	0.49	0.31-0.79	0.003	0.7	0	–	–	0.11

The rivaroxaban versus enoxaparin after total knee arthroplasty (RECORD) trial is another multicenter, double-blind trial that was published in 2009.[21] It randomized 3148 patients into two groups; 1584 were assigned to receive rivaroxaban 10 mg once daily and 1464 patients to receive enoxaparin 30 mg b.i.d. after total knee arthroplasty for the prophylaxis of VTE. It concluded that rivaroxaban reduced the total risk of VTE by 3.2% (absolute risk reduction is −3.19%, 95% CI − 0.67–7.71, $P = 0.0118$). Even though more events of bleeding (including major bleeding, and clinically relevant nonmajor bleeding) occurred in the rivaroxaban group, the difference compared to the enoxaparin group was not statically significant ($P = 0.1096$).

Apixaban (Eliquis Pfizer and Bristol Myers Squibb, New York City, NY, USA)

Apixaban is another selective, direct, factor Xa inhibitor. The FDA has approved its use for treatment of DVT and PE and for the prevention of recurrence after initial treatment in August 2014. The main route of its excretion is the hepatobiliary tract; its metabolism is medicated by cytochrome P450 enzymes, and 25% is excreted renally. Like rivaroxaban, inducers and inhibitors of the cytochrome enzymes as well as the P-gp enzymes should be avoided or used with caution when co-administered in patients receiving apixaban.

Apixaban peaks in the plasma 2–4 h after its administration; its half-life is 8 h for the 2.5 mg repeated dose and 15 h for the 5 mg single dose. It can be monitored by testing PT, aPTT, INR, and anti-factor Xa. Similar to the other NOACs, there is no specific antidote for apixaban, and usually cessation of therapy for 3 days is all that is required to reverse its action.[25] In cases of severe bleeding, the use of 4-factor PCC or activated PCC is recommended. Andexanet alpha (PRT4445) is a recombinant factor Xa protein that may be able to reverse partially the action of factor Xa inhibitors.[26] Phase II clinical trials are ongoing to evaluate this new medication as an antidote for rivaroxaban and apixaban.[27]

Apixaban was tested in a Phase II study, that is, efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis (Botticelli) trial [Table 6].[28] This study looked at different doses of apixaban in a group of 520 patients diagnosed with acute DVT.

This was followed by the apixaban for extended treatment of VTE (AMPLIFY) study [Table 6] that

Table 6: Apixaban for extended treatment of venous thromboembolism (AMPLIFY) study

Study:	BOTTICELLI N=520				AMPLIFY N=5,395					AMPLIFY-EXT N=2,482								
Duration of Treatment:	84-91 Days				10 mg BID for 7 Days, then 5 mg BID for 6 Months					12 Months								
Variable:	Apixaban 5 mg BID, %	Apixaban 10 mg BID, %	Apixaban 20 mg OD, %	Enoxaparin/ Warafarin, %	Apixaban, %	Enoxaparin/ Warfarin, %	Relative Risk, %	95% CI	P Value	Placebo, %	Apixaban 2.5 mg BID, %	Apixaban 5 mg BID, %	Relative Risk for 2.5 mg vs. Placebo	95% CI	P Value	Relative Risk for 5 mg vs. Placebo	95% CI	P Value
Primary efficacy outcome*	6.0	5.6	2.6	4.2	2.3	2.7	0.84	0.60-1.18	<0.001	11.6	3.8	4.2	0.33	0.22-0.48	<0.001	0.36	0.25-0.53	<0.001
Major and clinically relevant non-major bleeding	8.6	4.5	8.9	7.3	4.3	9.7	0.44	0.36-0.55	<0.001	2.7	3.2	4.3	1.20	0.69-2.10	–	1.62	0.96-2.73	–

was a randomized, double-blind study that compared apixaban to warfarin in the treatment of VTE in 5395 patients.[4] Apixaban dosing was 10 mg twice a day for 7 days, followed by 5 mg twice a day for 6 months. The primary efficacy outcome was recurrent symptomatic VTE or death related to VTE. The safety outcomes for all these trials were major bleeding and nonmajor bleeding that is clinically relevant. The primary efficacy outcome occurred in 2.3% in the apixaban arm as compared to 2.7% in the conventional therapy arm. The major bleeding occurred in 0.6% of patients who received apixaban and 1.8% of those who received conventional therapy. The composite outcome was 4.3% versus 9.7%. Bleeding profile was much improved in the apixaban group, specifically major bleeding. This led to the conclusion that a fixed dose of apixaban is a reasonable alternative to conventional therapy in the treatment of VTE and was associated with a significantly improved safety profile. The net clinical benefit of apixaban was 5.8%; 6.6% versus 12.4%. Thus, the number needed to treat the apixaban group to provide net clinical benefit is 17, so 17 patients would need to be treated with apixaban for 6 months to prevent one VTE, one VTE-related death, one major bleeding, and one nonmajor bleeding. The cost of novel anticoagulants ranges from 9.2 to 11.2 dollars/day. The net clinical benefit could cost between $28,543.00 and $34,748.00 for 6 months. This is based on the calculation of $9.2 \times 17 \times 182.5$ or $11.2 \times 17 \times 182.5$ for each first event of recurrent VTE, VTE-related death, major bleeding, or clinically irrelevant nonmajor bleeding. This underlies the importance to define groups, for whom cost-benefit calculation of treatment with apixaban will be most favorable.

Apixaban was also tested in the AMPLIFY-extension trial for prevention of VTE.[29] Reviewing the Kaplan–Meier curves for these trials showed that there was quite a significant lower risk of recurrent VTE in the group treated with apixaban, whether it is 2.5 mg or 5 mg b.i.d.; however, there was a slightly increased risk of bleeding. The arm that received 2.5 mg b.i.d. of apixaban had a very favorable bleeding profile, almost similar to the group that received a placebo. This led to the conclusion that extended anticoagulation with apixaban at 5 mg b.i.d. or 2.5 mg b.i.d. reduced the risk of VTE and had a favorable risk profile. The 2.5 mg b.i.d. dose was associated with a favorable bleeding profile [Table 7].

Table 7: Dose was associated with a favorable bleeding profile

Study:	RE-MEDY (N=2,856)					RE-SONATE (N=1,343)					EINSTEIN-EXTENSION (N=1,196)					AMPLIFY-EXT (N=2,482)						WARFASA (N=402)					ASPIRE (N=822)				
Duration:	6-36 Months					12 Months					6-12 Months					12 Months						2 Years					4 Years				
Variable:	Warfarin, %	Dabigatran, %	Hazard Ratio	95% CI	P Value	Placebo, %	Dabigatran, %	Hazard Ratio	95% CI	P Value	Rivaroxaban, %	Placebo, %	Hazard Ratio	95% CI	P Value	Placebo, %	Apixaban 2.5 mg BID, %	Apixaban 5 mg BID, %	Relative Risk for 2.5 mg vs. Placebo	95% CI	P Value	Aspirin, %	Placebo, %	Relative Risk for 5 mg vs Placebo	95% CI	P Value	Aspirin, %	Placebo, %	Hazard Ratio	95% CI	P Value
Recurrent VTE	1.3	1.8	1.44	0.78-2.64	0.01	5.6	0.4	0.08	0.02-0.25	<0.001	1.3	7.1	0.18	0.09-0.39	<0.001	11.6	3.8	4.2	.33	0.22-0.48	<0.001	6.6	11.2	0.36	0.25-0.53	<0.001	4.8	6.5	0.74	0.52-1.05	0.09
Major and clinically relevant non-major bleeding	10.2	5.6	0.54	0.41-0.71	<0.001	1.8	5.3	2.92	1.52-5.60	0.001	6.0	1.2	5.19	2.3-11.7	<0.001	2.7	3.2	4.3	1.20	0.69-2.10	–	1.9	2.0	1.62	0.96-2.73	–	1.1	0.6	1.72	0.72-4.11	0.22

Edoxaban (Lixana Daiichi Sankyo, Tokoyo, Japan)

Edoxaban is the newest factor Xa inhibitor, and the only one that is, not approved yet by the FDA for the treatment of VTE or for secondary prevention. It has a fast onset of action because of its rapid absorption (1–3 h).[30] It peaks in the plasma 1.5 h after its administration, and its half-life is 10–14 h for the 60 mg once daily dose. The kidney excretes 35% of edoxaban while 60% is excreted with feces; 70% of edoxaban is excreted unchanged. Monitoring the plasma concentration could be achieved by testing INR, PT, and anti-factor Xa activity. Reversal with recombinant human factor VIIa, anti-inhibitor coagulant complex (FEIBA), and PCC (PPSB-HT) is possible in preclinical studies.[31]

Edoxaban was recently listed in the Hokusai trial for the treatment of DVT.[5] This was a double-blind, double-dummy trial which looked at the low molecular weight heparin, followed by edoxaban at 60 mg daily (or 30 mg daily if CrCl is 30–50 ml/min, or if body weight is <60 kg) or if unfractionated heparin/low molecular weight heparin/warfarin was the conventional therapy. The duration of the study was <12 months and enrolled 4921 patients with DVT and 3319 patients with PE. The time in the therapeutic range for the warfarin arm was 63.5%. The edoxaban was noninferior to warfarin with respect to a primary efficacy outcome in the edoxaban group at 3.2% and 3.5% in the warfarin group. The safety outcome occurred in 8.5% in the edoxaban group and 10.3% in the warfarin group. Looking at the cumulative events and the Kaplan–Meier curve, the two arms were quite identical. Looking at the major clinically relevant and nonmajor bleeding, edoxaban had a favorable outlook and that led to the conclusion that edoxaban administered once daily offers a reasonable alternative treatment for patients with VTE. Surprisingly, from the Hokusai VTE trial, it was noted in the subgroup analysis for patients who were identified as having a large PE that these patients appeared to do better with edoxaban.

Aspirin

It is also important to mention the role of aspirin in the prevention of recurrent VTE. This was looked at in two recent trials: Low-dose aspirin for preventing recurrent VTE (WARFASA) and low-dose aspirin for preventing recurrent VTE (ASPIRE) trials, and the combination of these showed aspirin offered a modest decrease in the relative risk for recurrent VTE with only a slight increase in the risk of bleeding.[32,33] Thus, patients who are believed to be at low to moderate risk of VTE recurrence would benefit from a modest decrease at 32% risk reduction conferred by an aspirin 81 mg daily.

NOVEL ORAL ANTICOAGULANTS FOR EXTENDED TREATMENT OF VENOUS THROMBOEMBOLISM

Several studies looked at the extended duration of therapy in patients who are believed at moderate to high risk for recurrent VTE. These included the EINSTEIN-Extension, AMPLIFY-Extension, RE-SONATE, RE-MEDY, WARFASA, and ASPIRE trials.[4,6,29,32-35] The expected reduction was 70% for the EINSTEIN extension trial, followed by 41% for the AMPLIFY-extension, followed by the 70% reduction in the RE-SONATE trial, and then an absolute increase of <2.8 in the RE-MEDY trial. The WARFASA trial showed 40% expected reduction, and the ASPIRE trial showed about 30% reduction in risk of recurrent VTE.

Apixaban 2.5 mg twice a day showed similar efficacy for VTE prevention, yet bleeding risk was almost comparable to placebo. With VTE at 0.19, the hazard ratio for major bleeding was at 0.49 which presents a safe and quite effective medication for recurrent VTE in high-risk patients. Suggestions on the management of patients on chronic anticoagulation therapy with NOACs that require elective procedure are shown in Table 8.

CONCLUSION

With similar efficacy to warfarin and lower bleeding rates, the newer anticoagulants appear to be an attractive alternative to warfarin in the treatment of VTE. Combining all the data from six randomized clinical trials that studied the NOACs, a systematic review and meta-analysis by Kakkos *et al*. confirmed that NOACs are as effective as VKAs for preventing recurrent symptomatic VTE (RR 0.89, 95% CI 0.75–1.05) with lower incidence of major bleeding events (1.08% vs. 1.73% for VKAs, RR 0.63, 95% CI 0.51–0.77).[36] The same systematic review included three secondary prevention clinical trials. It concluded that NOACs reduced the rate for recurrent VTE to 1.32% (vs. 7.24% with placebo), the rate of fatal PE to 0.1% (vs. 0.29% for placebo), and the rate of all-cause mortality to 0.41% (vs. 0.86% with placebo). The number needed to treat was 18.

There are still many unanswered questions about the NOACs, and there will be more work needed to identify the best options for treatment in several groups of patients. For example, whether combining thrombolytics or antiplatelet (and perhaps dual antiplatelet) therapy and NOACs will increase the risk of bleeding, and the

investigational-antidote-pradaxa-dabigatran-etexilate-mesylate-fda-breakthrough-therapy-designation.html.

16. RXList. PRADAXA® (Dabigatran Etexilate Mesylate) Capsules for Oral Administration; 2014. Available from: http://www.rxlist.com/pradaxa-drug.htm.RXList.

17. Schulman S, Kakkar AK, Schellong SN. A Randomized Trial of Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER II). 53rd ASH Annual Meeting and Exposition. Session 332, Antithrombotic Therapy: New Anticoagulants ed. San Diego, CA: American Society of Hematology; 2011.

18. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, *et al.* Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.

19. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, *et al.* Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.

20. Janssen Pharmaceuticals I. Xarelto: Summary of Product Characteristics. Bayer Schering Pharma AG© Janssen Pharmaceuticals, Inc.; 2014. Available from: https://www.xarelto-us.com/?WHGRedir=1.

21. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): A randomised trial. Lancet 2009;373:1673-80.

22. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, *et al.* Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation 2007;116:180-7.

23. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

24. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, *et al.* Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.

25. Bristol-Myers Squibb Company. ELIQUIS (apixaban) Prescribing Information. Available from: http://www.packageinserts.bms.com/pi/pi_eliquis.pdf. [Last accessed on 2014 Aug].

26. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, *et al.* A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med 2013;19:446-51.

27. Crowther M, Vandana M, Michael K. A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Reversal of Rivaroxaban-Induced Anticoagulation in Healthy Subjects By Andexanet Alfa (PRT064445), An Antidote For Fxa Inhibitors 55th ASH Annual Meeting and Exposition. Abstracts, Program and Personal Scheduler ed. New Orleans, LA: American Society of Hematology; 2013.

28. Botticelli Investigators, Writing Committe, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost 2008;6:1313-8.

29. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.* Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.

30. Lip GY, Agnelli G. Edoxaban: A focused review of its clinical pharmacology. Eur Heart J 2014;35:1844-55.

31. Fukuda T, Honda Y, Kamisato C, Morishima Y, Shibano T. Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents. Thromb Haemost 2012;107:253-9.

32. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, *et al.* Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959-67. [Erratum appears in N Engl J Med 2012;367:1573].

33. Simes J, Becattini C, Agnelli G, Eikelboom JW, Kirby AC, Mister R, *et al.* Aspirin for the prevention of recurrent venous thromboembolism: The INSPIRE collaboration. Circulation 2014;130:1062-71.

34. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, *et al.* Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-87.

35. Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: The continued treatment study (EINSTEIN-extension study). Expert Rev Cardiovasc Ther 2011;9:841-4.

36. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice-efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: A systematic review and meta-analysis of phase III trials. Eur J Vasc Endovasc Surg 2014;48:565-75.

37. Pathak R, Pandit A, Karmacharya P, Aryal MR, Ghimire S, Poudel DR, *et al.* Meta-analysis on risk of bleeding with apixaban in patients with renal impairment. Am J Cardiol 2015;115:323-7.

38. 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;30:888-97.

39. Botticelli Investigators, Writing Committe, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost 2008;6:1313-8.

40. de Jesus GR, Agmon-Levin N, Andrade CA, Andreoli L, Chighizola CB, Porter TF, *et al.* 14th international congress on antiphospholipid antibodies task force report on obstetric antiphospholipid syndrome. Autoimmun Rev 2014;13:795-813.