

The novel anticoagulants: The surgeons' prospective

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Anticoagulants can complicate the approach to the management of patients undergoing operative interventions. We review new anticoagulants that have been introduced recently to the market or that are undergoing investigations for treatment of nonvalvular atrial fibrillation and venous thromboembolism prophylaxis: Dabigatran, rivaroxaban, apixiban, and edoxaban. (Surgery 2013;153:303-7.)

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MANY PATIENTS are on some form of “anticoagulation,” which complicate the operative approach to their management. Currently, >2.6 million Americans live with atrial fibrillation (AF), and the number may exceed 5.5 million by 2030. The estimated annual number of venous thromboembolism (VTE) in the United States is >300,000. Warfarin has been the drug of choice for over half a century for the long-term treatment of AF and VTE. New anticoagulants, however, have been introduced recently to the market or are undergoing investigations for nonvalvular AF and VTE prophylaxis.¹⁻³

WARFARIN: THE CURRENT MAINSTAY

Since its introduction in 1954, warfarin has been the most widely prescribed oral anticoagulant in the world. Warfarin inhibits vitamin K epoxide reductase in the liver, which inhibits production of the blood coagulation proteins factors II, VII, IX, and X, as well as proteins C and S. The inhibition of these 2 proteins contributes to the mild hypercoagulable phase seen early after initiation of warfarin. Warfarin has a narrow therapeutic window, which can be a challenge to both the health care provider as well as patients themselves. Warfarin is contraindicated in pregnancy and in

patients with underlying bleeding disorders. Other challenges for warfarin therapy are the many drug and dietary interactions. Drugs that are metabolized via the p450 cytochrome system can alter warfarin levels in the blood, hence, making warfarin difficult to control or maintain along with other medications. The most common clinical indications for warfarin are stroke prevention in AF and VTE, including deep venous thrombosis and pulmonary embolism.⁴ Warfarin has proven to be an effective anticoagulant for the past 5 decades, but has side effects and risks, especially in the elderly. This review addresses the safety and efficacy of some of the new oral agents (Fig 1; Table)

DABIGATRAN

Pharmacodynamics and pharmacokinetics. Dabigatran (Pradaxa; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT) is a selective, reversible direct thrombin (factor II) inhibitor currently used in Europe and North America for stroke prevention in nonvalvular AF and in Europe for VTE prophylaxis in orthopedic patients. Direct thrombin inhibitors decrease the amount of thrombin (the most important factor within the common coagulation pathway); hence, they inhibit the conversion of fibrinogen to fibrin and decrease clot formation.

Dabigatran acts rapidly and reaches effective levels within 2 hours after oral ingestion. It has selectivity and specificity to thrombin ($\leq 10,000$ -fold greater than any other major factors within the coagulation cascade). Dabigatran also inhibits tissue factor-induced thrombin generation in plasma, which is deficient in platelets and

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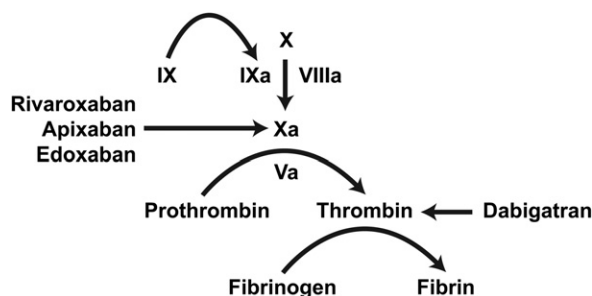


Fig 1. Coagulation cascade with targets of the new inhibitors.

decreases endogenous thrombin generation.⁵ Dabigatran is more effective than heparin because it blocks both free thrombin and fibrin-bound thrombin. Studies have shown that dabigatran is effective in preventing both venous thrombosis and arterial thrombosis. Converting the pro-drug to the active metabolite occurs partly in the liver. Most of the elimination of dabigatran occurs in the kidneys; therefore, dose adjustment is required in patients with renal impairment.^{6,7}

There is evidence for increased bleeding in patients over the age of 75 years.⁸ Dabigatran etexilate is a substrate for p-glycoprotein-drug transport protein “efflux pump” in the intestinal mucosa. Inhibition or induction of this pump can cause the peak plasma levels to increase or decrease, respectively. Quinidine is a potent inhibitor of dabigatran and is contraindicated with the use of dabigatran. Other inhibitors of the p-glycoprotein pump, such as ketoconazole, amiodarone, and verapamil, may cause increased levels. Dosage changes are not required while using these specific medications. Inducers of the p-glycoprotein pump decrease the plasma concentration of dabigatran, and avoidance is recommended by the manufacturer. Rifampin is a potent inducer that has been shown to decrease peak concentrations of dabigatran by 67%.⁹

Clinical efficacy and safety. Dabigatran has been shown to be effective in stroke prevention. Currently available in 2 doses (75 and 150 mg) dabigatran presently is only used in a small percentage of patients with AF. Dabigatran was approved for use in the United States based on the results of the RE-LY study, which enrolled >18,000 patients from 40 countries. The rate of major bleeding was 3.3% per year in the warfarin group, 2.7% per year in the group receiving 110 mg of dabigatran ($P = .003$), and 3.1% per year in the group receiving 150 mg dabigatran ($P = .31$). The rate of stroke or systemic embolism was 1.7% per year in the warfarin group, 1.5% per year in the group that received 110 mg dabigatran

($P < .001$ for noninferiority), and 1.1% per year in the group that received 150 mg dabigatran ($P < .001$ for superiority).¹⁰ Overall, there was more gastrointestinal bleeding and less intracranial hemorrhage in the dabigatran group. Myocardial infarction was slightly increased with both doses of dabigatran compared with warfarin (0.82% vs 0.64%) with a relative risk of 1.29.¹⁰ About 11% of patients receiving dabigatran had gastric dyspepsia believed to be owing to the pH of the drug, which lead to a greater rate of drug discontinuation and noncompliance.¹

Dabigatran has been studied in VTE prophylaxis after hip replacement in the RE-NOVATE, the RE-NOVATE II, the RE-MODEL, and the RE-MOBILIZE trials.^{11,12} Each study randomized between 2,000 and 3,000 patients comparing dabigatran with enoxaparin, all of which demonstrated noninferiority and less major bleeding. Treatment for deep venous thrombosis was analyzed in the RE-COVER, RE-SO-NATE, and RE-MEDY trials,^{13,14} and showed no differences between the traditional therapy and dabigatran.

A disadvantage of dabigatran is that there are currently no reversing agents. The management of patients with bleeding while receiving dabigatran should be according to the severity of bleeding: Those with moderate bleeding require blood transfusion, mechanical compression, and surgical intervention along with evaluation by nephrology to optimize the renal function is crucially important. In severe bleeding, recombinant factor VII or prothrombin complex concentrates could be considered (Fig 2). In patients undergoing elective surgery, dabigatran should be discontinued preoperatively 3–4 days when creatinine clearance is >50 mL/min, and 4–5 days when creatinine clearance is <50 mL/min. Discontinuation for a greater duration, because dabigatran is cleared by renal mechanisms, may be considered when performing high bleeding risk operations. Emergency operations in patients receiving dabigatran are associated with increased perioperative bleeding.¹⁵

RIVAROXABAN

Pharmacodynamics and pharmacokinetics. Rivaroxaban (Xarelto Janssen Pharmaceuticals, Titusville, NJ) is a direct, oral anti-Xa agent approved in Europe and North America for stroke prevention in nonvalvular AF and VTE prophylaxis. An oxazolidinone derivative, rivaroxaban binds to the active site of factor Xa blocking its function in the coagulation cascade. Rivaroxaban achieves maximum plasma levels at around 3 hours after ingestion. The half-life is 5–9 hours, but can be as long

Table. New anticoagulants with country of and indications for which it is approved

Anticoagulant	VTE prevention; orthopedic: THR, TKR	VTE prophylaxis nonorthopedic: surgery and medical patients	VTE treatment	Nonvalvular atrial fibrillation
Dabigatran (Pradaxa)	EU, Canada	None	None	EU, Canada, US
Rivaroxaban (Xarelto)	EU, Canada, US	None	DVT only in EU	EU, Canada, US
Apixaban (Eliquis)	EU, UK, US	None	None	None
Edoxaban	Japan	None	None	None

DVT, Deep venous thrombosis; EU, European Union; THR, total hip replacement; TKR, total knee replacement; UK, United Kingdom; US, United States; VTE, venous thromboembolism.

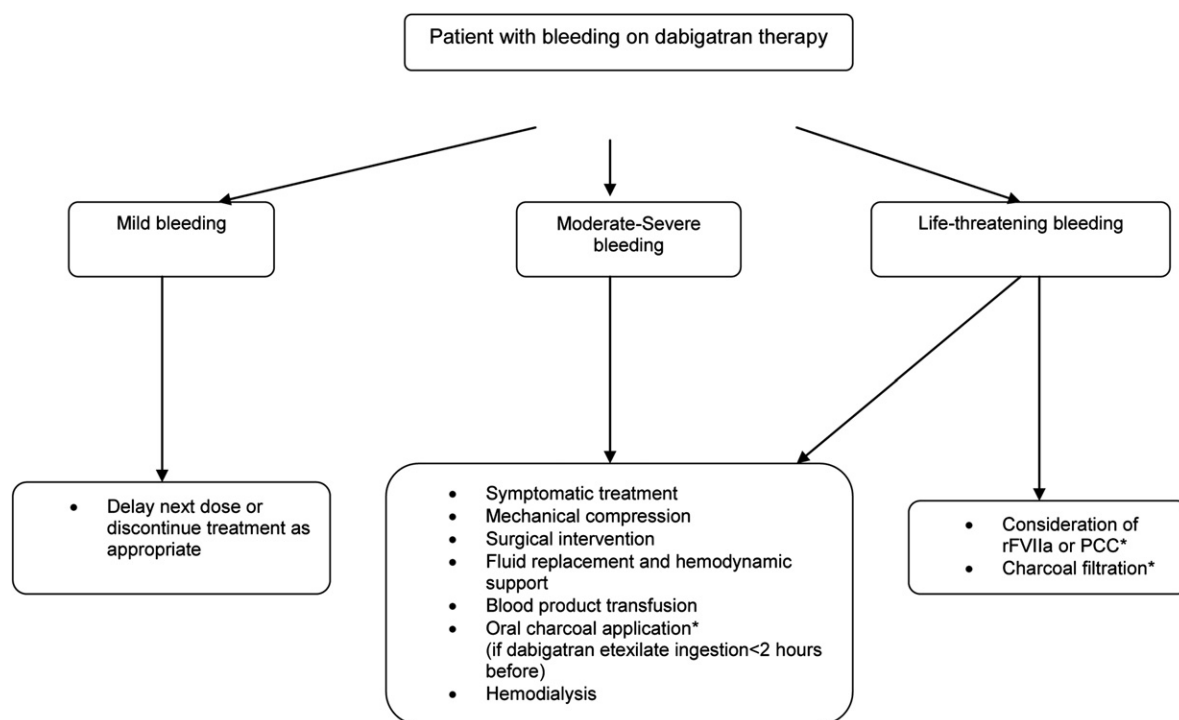


Fig 2. Management steps of bleeding in patients receiving dabigatran.

as 11–13 hours for those over age 75. The oral bioavailability is >80% for rivaroxaban. Although part of the elimination for rivaroxaban is in the liver, most of the elimination from the circulation occurs renally; therefore, dose adjustments in the elderly and in patients with chronic kidney disease may be necessary.¹⁶

A specific reversal agent for rivaroxaban is not available, and no clear data are available on how long it should be discontinued before elective operative procedures. In case of overdose, the use of activated charcoal to reduce absorption may be considered. Rivaroxaban is not dialyzable, because it possesses a high plasma protein binding effect. A single, blind, prospective, case control study assessed the efficacy of tranexamic acid in decreasing blood loss during

orthopedic operations in patients receiving rivaroxaban for thromboprophylaxis in this study showed a reduction of blood loss and a decrease in transfusion rate.¹⁷ Another European study described the possibility for prothrombin complex concentrate to serve as a potential antidote or reversal agent for rivaroxaban.¹⁸ Rivaroxaban is contraindicated for patients receiving azole antifungals (except fluconazole) or HIV protease inhibitors. Most of these drugs inhibit P-glycoprotein and CYP3A4 and can increase the levels of rivaroxaban.¹⁶

Clinical efficacy and safety. The ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) noninferiority trial enrolled >14,000

patients with nonvalvular AF randomly treated with a once daily dose of 20 mg rivaroxaban versus orally dose-adjusted warfarin. The primary endpoint was stroke or systemic embolism. The results demonstrated a 1.7% overall rate in the rivaroxaban group versus 2.2% in the warfarin group ($P < .001$). Although there was no difference in major bleeding between the 2 groups, intracranial bleeding occurred less with the rivaroxaban group (0.5% vs 0.7%) compared with the warfarin group ($P = .02$).¹⁹

Four phase III trials (RECORD I–IV) compared the efficacy and safety of 10 mg of rivaroxaban with 40 mg enoxaparin in >12,000 patients after total hip and knee arthroplasty. The once daily oral rivaroxaban had a greater efficacy with lesser incidence of symptomatic VTE and all-cause mortality (0.5% vs 1.3%). These trials did not show any significant difference in major bleeding between the 2 groups (0.3% vs 0.2%).^{20–22} The EINSTEIN-Medically ill trial of rivaroxaban versus LMWH in medically ill patients showed no net clinical benefit for rivaroxaban. The EINSTEIN-DVT and the EINSTEIN-PE made potentially important observations in the use of rivaroxaban for the treatment of VTE.^{23,24} The former trial showed less major bleeding (0.7% vs 0.1%) and less recurrent thromboembolic events (1.3% vs 1.07%). The latter trial showed less thromboembolism (2.1% vs 1.8%) and less major bleeding (2.2% vs 1.1%). Rivaroxaban also showed a mortality benefit when compared with optimal medical therapy in patients with acute coronary syndrome in the ATLAS-TIMI 46 trial.²⁵ Overall, it is believed that the usage of rivaroxaban may increase as physicians become more comfortable with this medication.

APIXIBAN

Pharmacodynamics and pharmacokinetics. Apixaban (Eliquis Pfizer and Bristol Myers Squibb, New York, NY) is a direct oral anti-Xa agent approved in Europe and North America for VTE prophylaxis in orthopedic patients undergoing surgery. Apixaban reaches maximum plasma levels at 3 to 4 hours and has a terminal half-life of 10–14 hours. In contrast, the elimination of apixaban is only 25% renally and 75% metabolized by the CYP3A4 and via the CYP-independent mechanisms of the liver. When apixaban is co-administered with ketoconazole, which is a strong inhibitor of CYP3A4 and P-glycoprotein, the mean apixaban level showed a 2-fold increase. Like rivaroxaban, it is contraindicated with the use of azole-antimycotics and HIV protease inhibitors. Naproxen, another P-glycoprotein inhibitor, caused the mean level of apixaban to increase.^{26,27}

Clinical efficacy and safety. The ARISTOTLE trial was a double-blind, randomized trial comparing apixaban with warfarin in >18,000 patients with nonvalvular AF. The study concluded fewer strokes and embolic events occurred in the apixaban group (1.27% vs 1.60%; $P < .01$); and fewer major bleeding events occurred (2.13 vs 3.09; $P < .001$). The study showed that there was a mortality benefit in the apixaban group.²⁸ Apixaban was compared with enoxaparin in the ADVANCE 1–3 trials for VTE prophylaxis after hip and knee arthroplasty and the ADOPT trial for medically ill patients; except for the latter study, thromboprophylaxis with apixaban was associated with lesser rates of venous thrombosis without increased bleeding.²⁹

EDOXABAN

Edoxaban (Lixana Daiichi Sankyo, Tokyo, Japan) is an oral, direct anti-Xa agent approved for use in Japan for VTE prophylaxis. This drug is also known as DU-176b is an oral direct Xa inhibitor currently in trials for AF, VTE, and arterial thromboembolism. Edoxaban has demonstrated a safety and efficacy profile comparable to warfarin in Phase I and II clinical trials.³⁰ In comparison with other anticoagulant medications, edoxaban shows some safety benefits and does not require constant monitoring. Additional clinical investigation of the efficacy and safety of edoxaban administered once daily is currently being conducted in phase III clinical trials.

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