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New anticoagulants: A concise review

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Abstract

During the last 2 years, two new oral anticoagulants, dabigatran and rivaroxaban, have been approved in the United States. Phase II and Phase III clinical trials of dabigatran, rivaroxaban, and apixaban are summarized. Approach to perioperative management depends on the half-life of the medication, risk of surgical bleeding, and the patient's renal function. No reversal agent is available for any of the neworal anticoagulants. Management of bleeding patients is based on local measures and consideration of antifibrinolytic therapy and activated factor VII or prothrombin complex concentrate infusion based on healthy volunteer and animal studies. The new oral anticoagulants provide additional options to prevent venous thromboembolism in patients after orthopedic surgery or stroke in patients with atrial fibrillation but present unique challenges compared to warfarin.

Keywords

Anticoagulation; thromboembolism; dabigatran; rivaroxaban; apixaban

Fifty-seven years since warfarin was approved by the US Food and Drug Administration (FDA), two new oral anticoagulants have entered the US market. These drugs have given patients and providers alternatives to heparin and warfarin for prophylaxis against stroke in patients with atrial fibrillation and venous thromboembolism (VTE) after orthopedic procedures. As more patients have switched to these anticoagulants, issues have arisen such as management of bleeding and perioperative management. This review will focus on dabigatran and rivaroxaban as they are approved for clinical use and apixaban as it has completed Phase III studies. The pharmacokinetic data for these agents are summarized in Table 1. A review of the coagulation cascade and the sites of action of these agents is seen in Figure 1. The new oral drugs are very effective anticoagulants because they inhibit proteins at the end of the coagulation cascade. Reversal of the anticoagulant effect is challenging because antidotes for these anticoagulants do not exist. This review will summarize

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available clinical trial evidence and a proposed approach to management of bleeding and the perioperative setting.

DABIGATRAN

Clinical Trials

Dabigatran is an oral direct thrombin inhibitor that is FDA approved for stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation. The RE-LY trial randomized more than 18,000 patients with nonvalvular atrial fibrillation to blinded treatment with dabigatran 150 mg or 110 mg orally twice a day (BID) or open-label warfarin (Table 2). Dabigatran 150 mg was superior to warfarin in prevention of stroke or systemic embolism with the primary end point occurring in 1.11% per year of patients managed with dabigatran compared with 1.69% per year in patients treated with warfarin (p G 0.001 superiority). The 110-mg dose was noninferior to warfarin. The rate of ischemic stroke was significantly less only in patients treated with 150 mg of dabigatran. Life-threatening hemorrhage occurred less often with either dose of dabigatran. Intracranial hemorrhage occurred significantly less in the dabigatran 110-mg and 150-mg groups compared with warfarin with a rate of 0.23% per year, 0.3% per year, and 0.74% per year, respectively.[1] The FDA approved dabigatran (Pradaxa; Boehringer Ingelheim, Ingelheim, Germany) 150 mg orally BID in October 2010 for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The 110-mg dose was not approved as subset analyses did not find a group in which the risk-benefit profile was superior to the 150-mg dose.[2] Based on pharmacokinetic data, 75 mg orally BID was approved for patients with creatinine clearances between 15 mL per minute and 30 mL per minute, but other authors suggest caution with use in this group.[3] Subsequent analysis has shown that poorly controlled patients on warfarin with international normalized ratio (INR) measurements in therapeutic range less than 65% of the time benefited the most and may be the best candidates for dabigatran therapy.[4]

A phase II placebo-controlled dose escalation study (50Y150 mg BID) of dabigatran in patients after myocardial infarction showed equal rates of cardiovascular death, myocardial infarction, and stroke, but a dose-dependent increase in bleeding rates.[5] Additional studies of dabigatran for secondary prevention after acute coronary syndromes are not currently available.

Dabigatran has also been studied in prophylaxis of VTE after knee and hip replacement. The RE-MODEL and REMOBILIZE trials compared 150 mg and 220 mg of dabigatran with enoxaparin 40 mg per day subcutaneously or 30 mg BID subcutaneously, respectively. Both dabigatran doses were found to have equal bleeding rates in comparison with enoxaparin. However, enoxaparin 30 mg BID was superior to dabigatran, whereas dabigatran was noninferior to enoxaparin 40 mg per day (Table 2).[6] In a study of 2,000 patients treated after total hip replacement, VTE or death occurred in 2.2% of patients treated with dabigatran 220 mg compared with 4.2% of patients treated with enoxaparin 40 mg per day (risk difference, −1.9%; p = 0.03 superiority). Major bleeding was similar between the groups (1.4% dabigatran, 0.9% enoxaparin; p = 0.4).[7] Overall, these data suggest similar efficacy to enoxaparin 40 mg per day in VTE prophylaxis after orthopedic surgery with a similar

bleeding risk. Dabigatran has been approved in Europe and Canada for prevention of VTE after orthopedic surgery based on these data.

The RE-COVER trial examined the use of dabigatran to treat VTE in 2,500 patients with proximal deep vein thrombosis or pulmonary embolism. All patients were treated with low-molecular-weight heparin and then randomized to dabigatran 150 mg BID or warfarin for 6 months in a double-blind, double-dummy design. Recurrent VTE occurred in 2.4% in the dabigatran arm and 2.1% in the warfarin group (p G 0.001, noninferiority). Major bleeding was equal, but the location of bleeding was more often in a critical organ (nine intracranial hemorrhages with warfarin vs. one intracranial hemorrhage with dabigatran). The incidence of any bleeding was also higher in thewarfarin group (21.9 vs. 16.1%; hazard ratio [HR], 0.71).[8] The RE-MEDY trial is an extension of the RE-COVER trial examining the use of dabigatran for secondary prevention of VTE. The study was completed in October 2010, and we anticipate results in the next year.

Laboratory Testing

One of the major benefits of dabigatran over warfarin is that laboratory monitoring is not required during therapy. However, there are many instances in which knowing the degree of anticoagulation is paramount. For patients on dabigatran, the activated partial thromboplastin time (aPTT) increases with larger doses; however, the dose response is not linear and plateaus at higher concentrations of dabigatran.[3,9] The prothrombin time (PT/INR) is variably affected but has been shown to rise with therapeutic doses.[9] The INR is an insensitive measure of dabigatran activity and should not be used to monitor patients. Elevations in activated clotting time measured by thromboelastography (TEG) have been reported,[10] but animal studies showed similar TEG profiles in pigs on dabigatran and without anticoagulation.[11] The thrombin time (TT) measures the direct activity of thrombin and is the most sensitive to the effects of dabigatran. If the TT is normal, there is no dabigatran in the sample. At high concentrations of dabigatran, however, the thrombin time may be above a measurable level. The ecarin clotting time (ECT) also directly measures the anticoagulant effect of direct thrombin inhibitors but is less sensitive than the TT, thus, a more accurate measure of the concentration of dabigatran. The ECTis not widely available, thus, most hospitals may be limited to aPTT and TT to interpret the extent of anticoagulation in patients on dabigatran.[3]

RIVAROXABAN

Clinical Trials

Rivaroxaban is an oral direct inhibitor of activated factor X (Xa) that is FDA approved for stroke and systemic embolization prevention in nonvalvular atrial fibrillation and VTE prevention after knee and hip replacement. The ROCKET-AF trial randomized more than 14,000 patients with atrial fibrillation and two stroke risk factors to rivaroxaban 20 mg per day or warfarin (Table 3). Rivaroxaban was noninferior to warfarin in the prevention of stroke and systemic embolism (2.1% per year rivaroxaban vs. 2.4% per year warfarin, p G 0.001 noninferiority). Major bleeding was equal between the rivaroxaban and warfarin groups at 5.6% and 5.4%, respectively. Fatal bleeding was 50% lower in the rivaroxaban

group (0.4% vs. 0.8%, p = 0.003). Intracranial hemorrhage rates were also decreased with rivaroxaban (0.8% vs. 1.2%, p = 0.02).[12] Rivaroxaban was approved for prevention of stroke in patients with nonvalvular atrial fibrillation in November 2011 (20 or 15 mg per day orally if creatinine clearance 15Y50 mL per minute).[13] After discontinuation of rivaroxaban in the ROCKET-AF trial, an increased risk of stroke was found, leading to a black box warning.[13] To maintain blinding in the trial at its completion, patients were not bridged when switching from rivaroxaban to warfarin. Inadequate anticoagulation in high-risk patients likely led to increased stroke risk.

The ATLAS-TIMI 46 and 51 studies used rivaroxaban in patients after acute coronary syndromes to reduce cardiovascular end points.[14,15] Compared with placebo, rivaroxaban decreased the composite end point of cardiovascular death, myocardial infarction, and stroke but caused a significantly higher major bleeding. The use of rivaroxaban after acute coronary syndromes currently is not standard of care.

In the RECORD trials, rivaroxaban was compared with enoxaparin for VTE prophylaxis after total knee and hip replacement.[16-19] Rivaroxaban 10 mg per day orally was found to be superior to enoxaparin 40 mg per day and 30 mg BID. In a systematic review of these studies, the relative risk of VTE was 0.38 compared with that of enoxaparin 40 mg per day (p < 0.0001) and 0.77 in comparison with enoxaparin 30 mg BID (p = 0.05). No significant difference in postoperative bleeding was noted. In all of these studies, rivaroxaban was started within 6 to 8 hours of surgery and continued for an average of 12 days after knee replacement and 35 days after hip replacement.[20] In July 2011, the FDA approved rivaroxaban (Xarelto; Janssen Pharmaceuticals, Titusville, NJ) for VTE prophylaxis after orthopedic surgery.

Rivaroxaban has also been tested against warfarin in the treatment of VTE. The EINSTEIN trial was an open-label randomized noanferiority study of rivaroxaban 15 mg BID for 3 weeks then 20 mg per day compared with enoxaparin bridged to warfarin. Recurrent VTE occurred in 3% of patients treated with enoxaparin/warfarin and 2.1% patients treated with rivaroxaban (p < 0.001 noninferiority). Major and clinically relevant bleeding was similar between the groups (major bleed 0.8% rivaroxaban vs. 1.2% enoxaparin/warfarin; p = 0.21). The EINSTEIN extension study showed that rivaroxaban was effective for secondary VTE prophylaxis, with recurrent VTE in 7.1% of the placebo group versus 1.3% on rivaroxaban (p < 0.001). Major bleeding occurred in 0.7% of patients on rivaroxaban and zero patients on placebo (p = 0.11).[21] This suggests that bleeding risk is low with rivaroxaban, but comparison to bleeding rates for long-term anticoagulation on warfarin would require extrapolation from other studies.

Laboratory Testing

Routine laboratory monitoring of rivaroxaban is not required. As factor is a part of the common coagulation pathway, inhibitors of factor Xa should prolong the PT and aPTT. The degree of prolongation is dependent on the reagent used. No effect was seen on the TT or fibrinogen activity assays.[22] Dose dependent prolongation of TEG parameters (R and K times) has been reported.[23] Chromogenic anti-Xa assays can be standardized to measure rivaroxaban, but this test may not be routinely available.[24]

APIXABAN

Clinical Trials

Apixaban is an oral direct factor Xa inhibitor that has completed several phase III trials but has not yet been approved by the FDA (Table 4). Apixaban has been studied in two large trials in patients with atrial fibrillation. The AVERROES trial randomized 5,600 patients unsuitable for warfarin therapy to apixaban 5 mg BID versus aspirin. With a mean follow-up of 1.1 years, the trial was stopped early for benefit as the rate of stroke or systemic embolism was 3.7% per year in the aspirin group versus 1.6% per year with apixaban. Similar rates of bleeding were seen in both treatment groups including rates of intracranial hemorrhage (0.4% per year in both groups).[25] This trial has been criticized because of the lack of standardization of the aspirin dose and the use of enteric-coated aspirin. The ARISTOTLE trial compared apixaban 5mg BID with warfarin in more than 18,000 patients with atrial fibrillation and one stroke risk factor. Apixaban was superior to warfarin in prevention of stroke or systemic embolization. The rate of hemorrhagic stroke was reduced by one half with apixaban (0.24% per year apixaban vs. 0.47% per year warfarin; $p < 0.001$). The rate of death from any cause was also lower in the apixaban group (HR, 0.89; $p = 0.047$). Intracranial hemorrhage was reduced from 0.8% per year with warfarin to 0.33% per year with apixaban ($p < 0.001$). Major bleeding occurred significantly less often with apixaban compared with warfarin and a 7.7% absolute risk reduction for all bleeding was noted with apixaban ($p < 0.001$).[26] Overall, apixaban appears to be an effective alternative to warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation.

A Phase II and III study tested the use of apixaban with antiplatelet therapy after acute coronary syndromes.[27,28] The APPRAISE-2 studywas discontinued early because of increased major bleeding without a decrease in the composite primary end point of cardiovascular death, recurrent myocardial infarction, and stroke.

Apixaban has been evaluated in prevention but not treatment of VTE. The ADVANCE trials have examined the use of apixaban 2.5 mg BID versus enoxaparin in prophylaxis of VTE after orthopedic surgery. When compared with enoxaparin 30 mg BID, apixaban failed noninferiority to enoxaparin with rates of VTE and all-cause mortality in 9% of the apixaban and 8.9% of the enoxaparin groups.[29]

However, when compared with the European regimen of enoxaparin 40 mg per day, apixabanwas found to be superior with equal bleeding rates after total knee and hip replacement.[30,31]

Laboratory Testing

Apixaban has a mechanism of action similar to rivaroxaban with direct inhibition of factor Xa. Apixaban also prolongs the aPTT and PT levels with variability in the PT depending on the reagents used in testing. The linear correlation of the plasma concentration of apixaban and anti-Xa levels standardized to apixaban or to low-molecular-weight heparin are equally strong ($r = 0.967$). Therefore, recalibration of anti-Xa testing may not be necessary to determine the degree of anticoagulation with apixaban.[32]

MANAGEMENT OF BLEEDING WITH NEW ORAL ANTICOAGULANTS

The bleeding rates with the new oral anticoagulants are generally equal to or less than bleeding rates with warfarin, but antidotes are not available. Figure 1 shows the sites of action of the neworal anticoagulants and hemostatic agents that could be used. Algorithms for managing hemorrhage in patients on dabigatran have been developed.[33] A proposed management guideline is presented in Figure 2.

Initial evaluation for bleeding patients on the new oral anticoagulants includes an assessment of hemodynamic stability, severity of bleeding, and level of anticoagulation. Life threatening bleeding (i.e., intracranial hemorrhage) requires the most aggressive response. Baseline clotting times, fibrinogen activity, complete blood count, creatinine, and liver function tests should be obtained. Alteration in renal function will affect the metabolism of dabigatran the most and apixaban the least. Apixaban and rivaroxaban metabolism is altered by changes in liver function. Assessment for anatomic etiology of the hemorrhage should be sought with use of local control measures if possible. Activated charcoal will decrease absorption of the anticoagulants if administered within 2 to 3 hours of ingestion of the anticoagulant. Dialysis will remove dabigatran because of its low plasma protein binding, whereas rivaroxaban and apixaban are likely not dialyzable.[3,34] The volume of distribution of dabigatran is large (60-70 L);[3] therefore, multiple sessions of dialysis may be required. Extrapolating from the trauma literature, if massive transfusion is required, we recommend transfusion in 1:1 plasma:packed red blood cell ratio to prevent dilutional and consumptive coagulopathy.[35]

In cases of significant bleeding, additional hemostatic agents should be considered (Table 5). Antifibrinolytic medication provides clot stabilization if fibrin is able to form. In a large randomized trial of injured patients not taking the new oral anticoagulants, tranexamic acid was shown to decrease the risk of death caused by hemorrhage when given within the first 3 hours of injury.[36] Antifibrinolytic agents have been ineffective in reducing bleeding times with direct thrombin inhibitors and may not be useful for patients taking dabigatran.[3] A recent prospective case series suggests decreased postoperative blood loss in patients treated with both rivaroxaban prophylaxis and tranexamic acid.[37] Reversal agents for the new oral anticoagulants including an inactivated Xa product are in development but are not currently available.[38] In healthy subjects, the anticoagulant effect of rivaroxaban can be reversed with administration of 50 units/kg of Cofact (Sanquin; Amsterdam, Netherlands), a nonactivated four-factor prothrombin complex concentrate (PCC) (Table 5). In patients on dabigatran, clotting times remained prolonged after PCC infusion, showing inadequate reversal of anticoagulation effect.[39] In a rat tail model of bleeding, recombinant activated factor VII, nonactivated four-factor PCC, and activated PCC were shown to significantly reduce bleeding times in dabigatran-treated animals.[3,40] Laboratory coagulation tests did not predict the reversal of bleeding in the mice, however.[40] In a mouse model of intracranial hemorrhage with dabigatran use, a nonactivated fourfactor PCC prevented hematoma expansion, but activated factor VII did not have an effect.[41] Clinical data on dabigatran and rivaroxaban reversal using PCCs and activated factor VII in humans are not available. In addition, four-factor PCCs are not available in the United States (Table 5). Thrombosis and disseminated intravascular coagulation have occurred with administration of activated factor

VII and activated and nonactivated PCCs. Therefore, the risk of hemorrhage needs to be weighed against the risk of using any of these procoagulant agents and patients must be monitored closely.

PERIOPERATIVE MANAGEMENT

Timing of anticoagulant discontinuation before surgery depends on the half-life of the anticoagulant, the patient's renal function, and the surgical risk of bleeding. Creatinine clearance plays the largest role in perioperative management of dabigatran. Table 6 summarizes recommendations regarding timing of discontinuation in standard risk procedures. High-risk procedures including cardiac surgery, neurosurgery, abdominal surgery, or procedures requiring spinal anesthesia may require 2 to 4 days off dabigatran in patients with normal renal function and 4 days off therapy with creatinine clearance 30 to 50 mL per minute.[3] Checking an ECT or TT in patients with renal impairment on dabigatran is an option to ensure that minimal anticoagulant effect remains before the procedure. Rivaroxaban has a significantly shorter half-life than dabigatran and thus could be discontinued 24 hours before surgery.[13] The half life of rivaroxaban in elderly patients increases, so 48 hours may be necessary to allow for proper elimination. An increased risk of stroke has been reported after discontinuation of rivaroxaban, thus, minimizing the duration without anticoagulation in high-risk patients is recommended.[13] In elderly patients, higher levels of apixaban have been reported. Providers should consider discontinuing apixaban for 48 hours or checking an anti-Xa level before surgery.[42]

Timing of resumption of the new anticoagulants after surgery is dependent on bleeding risks and the dose used. It is important to remember that these drugs fully anticoagulate the patient in 2 to 4 hours. In clinical trials for VTE prophylaxis after orthopedic surgery, dabigatran was initiated at one-half dose 1 to 4 hours after surgery and full dose 12 hours later.[6] Rivaroxaban was initiated 6 to 8 hours after wound closure and apixaban was started 12 to 24 hours postoperatively.[20,43] For procedures with a low bleeding risk, full anticoagulation with apixaban could be restarted after 24 hours, whereas resumption of anticoagulation after major surgery could be considered 48 hours postoperatively. 43 Additional clinical data and experience with the new anticoagulants will influence perioperative and postoperative management in the future.

CONCLUSIONS

Two new oral anticoagulants are available in the United States with additional agents likely to be approved in the near future. Each of these agents has the benefit of oral administration and uniform dosing. A majority of the clinical benefit is likely secondary to consistent anticoagulant effect. Monitoring of anticoagulant activity is not required but may be necessary in specific instances such as bleeding. Determining the anticoagulant effect of dabigatran requires special coagulation testing using the TT or ECT. Rivaroxaban and apixaban can be monitored through standardized anti-Xa assays. Perioperative and postoperative management of anticoagulation should be determined by the surgical risk of bleeding and renal function of the patient, which may be affected by age. In the bleeding patient, reversal of anticoagulant effect depends on the severity of hemorrhage and hepatic

and renal function, which will determine the metabolism of the drugs. In healthy volunteers, PCC can reverse the effects of rivaroxaban, but it is unknown if this can be extrapolated to bleeding individuals on any Xa inhibitor if severe hemorrhage occurred. Reversal of dabigatran with activated PCC and factor VII has only been shown in animals. Until additional clinical data become available, physicians will need to rely on a hemorrhage management algorithm and clinical judgment.

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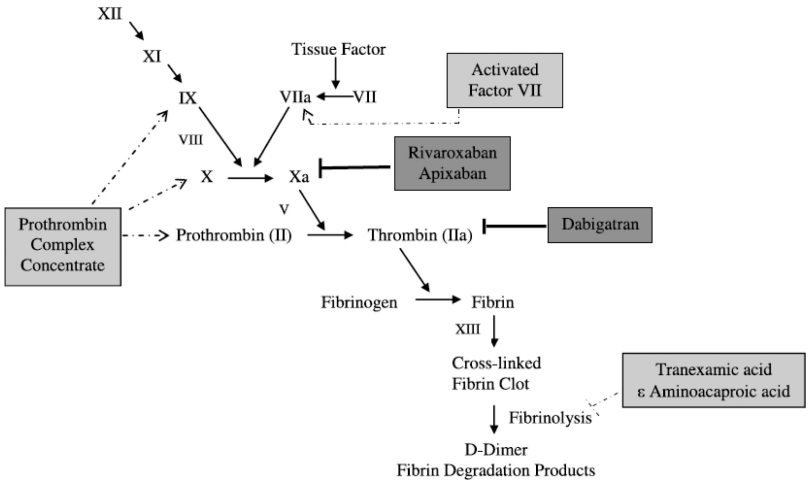

Figure 1.

Clotting cascade and location of activity of new oral anticoagulants and hemostatic agents. Proteins are depicted by their zymogen symbols. The new oral anticoagulants are depicted in dark gray boxes with bold inhibition lines. Hemostatic agents are in light gray boxes with dashed lines in the area of activity. The PCC is depicted as containing nonactivated proteins for simplicity but can contain activated proteins and factor VII also depending on the product.

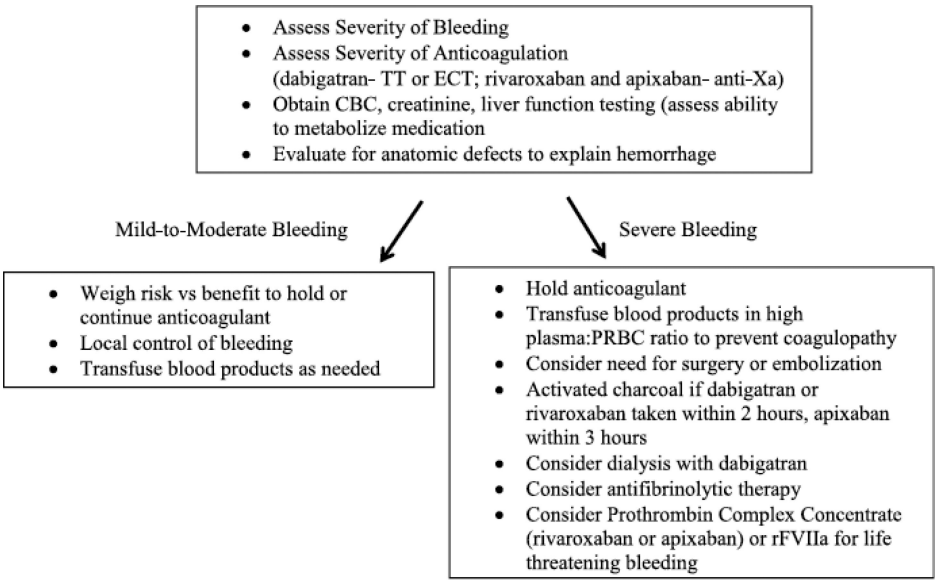

Figure 2.
Management guideline for bleeding while taking dabigatran, rivaroxaban, or apixaban.

TABLE 1

Pharmacokinetic Properties of New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
FDA-approved indications	Prevention of stroke and systemic embolism in nonvalvular atrial fibrillation	VTE prophylaxis after hip and knee replacement, stroke and systemic embolism prophylaxis in nonvalvular atrial fibrillation	Pending
Activity	Inhibits free and clot bound thrombin (factor IIa)	Inhibits factor Xa	Inhibits factor Xa
Dosing for atrial fibrillation	150 mg BID, 75 mg BID if CrCl 15Y30 mL/min	20 mg/d, 15 mg/d if CrCl 15Y50 mL/min	5 mg BID‡
Dosing for VTE prophylaxis		10 mg/d	2.5 mg BID‡
Onset of action	1.5-3 h	2-4 h	3 h
Half-life	14-17 h	5-9 h, 11-13 h elderly§	8-15 h
Metabolism and excretion	80% renal, 20% fecal	66% renal, 33% fecal	25% renal 75% biliary, fecal
Drug Interactions	P-glycoprotein inhibitors*	Potent CYP3A4 inhibitors†, P-glycoprotein inhibitors*	Potent CYP3A4 inhibitors†, P-glycoprotein inhibitors*
Detection of anticoagulant effect	ECT if available, TT most sensitive	Anti-Xa assay	Anti-Xa assay
Unique issues	Must be stored in original bottle	Highly protein bound and not dialyzable, take with evening meal	Highly protein bound and not dialyzable

*Rifampin, amiodarone.

†Ketoconazole, itraconazole, voriconazole, ritonavir.

‡Dosing not approved by FDA.

§Despite half-life, daily dosing because of persistence of anti-Xa activity. CrCl, creatinine clearance.

TABLE 2

Phase II and III Clinical Trials Using Dabigatran

Trial Name	Indication	Dabigatran Dose	Comparator	Treatment Duration	Thrombotic Outcome	Major Bleeding
PETRO[44] Phase II	Nonvalvular atrial fibrillation	50 mg, 150 mg or 300 mg BID	Warfarin (INR 2Y3)	12 wk	Stroke and systemic embolism 50 mg: 1.7% 150 mg: 0% 300 mg: 0% Warfarin: 0%	50 mg: 0% 150 mg: 0% 300 mg: 0% Warfarin: 0%
RE-LY[1] Phase III	Nonvalvular atrial fibrillation	110 mg or 150 mg BID	Warfarin (INR 2Y3)	Median follow-up 2 y	Stroke and systemic embolism 110 mg: 1.53%/y‡ 150 mg: 1.11%/y* Warfarin: 1.69%/y	110 mg: 2.71%/y* 150 mg: 3.11%/y Warfarin: 3.36%/y
RE-DEEM[5] Phase II	Secondary prevention after ACS	50 mg, 75 mg, 110 mg, 150 mg BID	Placebo	6 mo	CV death, MI, or stroke 50 mg BID: 4.6% 75 mg BID: 4.9% 110 mg BID: 3.0% 150 mg BID: 3.5% placebo: 3.8%	50 mg BID: 0.8% 75 mg BID: 0.3% 110 mg BID: 2.0%† 150 mg BID: 1.2%† placebo: 0.5%
BISTRO I[45] Phase II	VTE prevention after THR	Dose escalation 12.5Y300 mg twice daily, 150 mg or 300 mg/d	N/A	6Y10 d	All VTE 12.5 mg BID: 20.8% 25 mg BID: 9.5% 50 mg BID: 14.8% 100 mg BID: 19.4% 150 mg Daily: 9.1% 150 mg BID: 9.5% 200 mg BID: 19.0% 300 mg Daily: 0%	0% in all groups
BISTRO II[46] Phase II	VTE prevention after THR or TKR	50 mg, 150 mg, or 225 mg twice daily, 300 mg/d	Enoxaparin 40 mg/d	6Y10 d	All VTE 50 mg BID: 28.5% 150 mg BID: 17.4%* 300 mg/d: 16.6%* 225 mg BID: 13.1%* Enoxaparin: 24%	50 mg BID: 0.3%* 150 mg BID: 4.1% 300 mg/d: 4.7% 225 mg BID: 3.8% Enoxaparin: 2%
RE-MODEL[47] Phase III	VTE prevention after TKR	150 mg or 220 mg/d	Enoxaparin 40 mg/d	6Y10 d	VTE and all-cause mortality 150 mg: 40.5%‡ 220 mg: 36.4%‡ Enoxaparin: 37.7%	150 mg: 1.3% 220 mg: 1.5% Enoxaparin: 1.3%
RE-NOVATE[48] Phase III	VTE prevention after THR	150 mg or 220 mg/d	Enoxaparin 40 mg/d	28Y35 d	VTE and all-cause mortality 150 mg: 8.6%‡ 220 mg: 6%‡ Enoxaparin: 6.7%	150 mg: 1.3% 220 mg: 2% Enoxaparin: 1.6%
RE-MOBILIZE[49] Phase III	VTE prevention after TKR	150 mg or 220 mg/d	Enoxaparin 30 mg BID	12Y15 d	VTE and all-cause mortality 150 mg: 34%† 220 mg: 31%† Enoxaparin: 25%	150 mg: 0.6% 220 mg: 0.6% Enoxaparin: 1.4%
RE-NOVATE II[7] Phase III	VTE prevention after THR	220 mg/d	Enoxaparin 40 mg/d	208Y35 d	VTE and all-cause mortality 220 mg: 7.7%‡ Enoxaparin: 8.8%	220 mg: 1.4% Enoxaparin: 0.9%
RE-COVER[8] Phase III	Acute VTE treatment	150 mg BID	Warfarin (INR 2Y3)	6 mo	Recurrent VTE Dabigatran: 2.4%‡ Warfarin: 2.1%	Dabigatran: 1.6% Warfarin: 1.9%
RE-MEDY Phase III	Secondary VTE prophylaxis	150 mg BID	Warfarin (INR 2Y3)	18 mo	Not reported	Not reported

ACS, acute coronary syndrome; TKR, total knee replacement; THR, total hip replacement.

* Statistically significant superiority demonstrated over comparator.

† Statistically significant inferiority demonstrated over comparator.

‡ Statistically significant noninferiority demonstrated to comparator.

TABLE 3

Phase II and III Clinical Trials Using Rivaroxaban

Trial Name	Indication	Rivaroxaban Dose	Comparator	Treatment Duration	Thrombotic Outcome	Major Bleeding
ROCKET-AF[12] Phase III	Nonvalvular atrial fibrillation	20 mg/d	Warfarin (INR 2Y3)	Median treatment 19.7 mo	Stroke and Systemic embolism Rivaroxaban: 2.12%/y[‡] Warfarin: 2.42%/y	Rivaroxaban: 3.6%/y Warfarin: 3.4%/y
ATLAS ACS-TIMI 46[14] Phase II	Secondary prevention after ACS	5Y20 mg/d total dose	Placebo	6 mo	CV death, MI, stroke, revascularization 5 mg: 5.8% 10 mg: 3.8% 15 mg: 6.2% 20 mg: 5.5% Placebo: 5.1%	5 mg: 0.7%[†] 10 mg: 1.5%[†] 15 mg: 1.8%[†] 20 mg: 1.8%[†] Placebo: 0.1%
ATLAS ACS-TIMI 51[15] Phase III	Secondary prevention after ACS	2.5 mg and 5 mg BID	Placebo	31 mo	CV death, MI, stroke 2.5 mg BID: 9.1%[*] 5 mg BID: 8.8%[*] Placebo: 10.7%	2.5 mg BID: 1.8%[†] 5 mg BID: 2.4%[†] Placebo: 0.6%
RECORD1[16] Phase III	VTE prevention after THR	10 mg/d	Enoxaparin 40 mg/d	31 Y39 d	VTE and all-cause mortality Rivaroxaban: 1.1%[*] Enoxaparin: 3.7%	Rivaroxaban: 0.3% Enoxaparin: 0.1%
RECORD2[17] Phase III	VTE prevention after THR	10 mg/d	Enoxaparin 40 mg/d	31Y39 d, enoxaparin 10Y14 d	VTE and all-cause mortality Rivaroxaban: 2%[*] Enoxaparin: 9.3%	Rivaroxaban: G0.1% Enoxaparin: G0.1%
RECORD3[18] Phase III	VTE prevention after TKR	10 mg/d	Enoxaparin 40 mg/d	10Y14 d	VTE and all-cause mortality Rivaroxaban: 9.6%[*] Enoxaparin: 18.9%	Rivaroxaban: 0.6% Enoxaparin: 0.5%
RECORD4[19] Phase III	VTE prevention after TKR	10 mg/d	Enoxaparin 30 mg BID	10Y14 d	VTE and all-cause mortality Rivaroxaban: 6.9%[*] Enoxaparin: 10.1%	Rivaroxaban: 0.7% Enoxaparin: 0.3%
MAGELLAN[50] Phase III	VTE medical patients	10 mg/d	Enoxaparin 40 mg daily	35Y39 d, enoxaparin 10Y14 d	VTE death and all VTE Rivaroxaban: 4.4%[*] Enoxaparin: 5.7%	Rivaroxaban: 1.1%[†] Enoxaparin: 0.4%
ODIXa-DVT[51] Phase II	Acute VTE treatment	10 mg, 20 mg, 30 mg BID or 40 mg/d	Enoxaparin/warfarin (INR 2Y3)	12 mo	Thrombotic burden and VTE death 10 mg BID: 53% 20 mg BID: 59.2% 30 mg BID: 56.9% 40 mg: 43.8% Warfarin: 45.9%	10 mg BID: 1.7% 20 mg BID: 1.7% 30 mg BID: 3.3% 40 mg: 1.7% Warfarin: 0%
EINSTEIN[21] Phase III	Acute VTE treatment	15 mg BID for 3 wk, 20 mg/d	Enoxaparin/warfarin (INR 2Y3)	3Y12 mo	Recurrent VTE Rivaroxaban: 2.1%[‡] Warfarin: 3.0%	Rivaroxaban: 0.8% Warfarin: 1.2%

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ACS, acute coronary syndrome; MI, myocardial infarction; THR, total hip replacement; TKR, total knee replacement.

* Statistically significant superiority demonstrated over comparator.

† Statistically significant inferiority demonstrated over comparator.

‡ Statistically significant noninferiority demonstrated to comparator.

TABLE 4

Phase II and III Clinical Trials of Apixaban

Trial Name	Indication	Dose	Comparator	Treatment Duration	Thrombotic Outcome	Major Bleeding
AVERROES[25] Phase III	Nonvalvular atrial fibrillation	5 mg BID	Aspirin 81Y324 mg	Median follow-up 1.1 y	Stroke or systemic embolism Apixaban: 1.6%/y * Aspirin: 3.7%/y	Apixaban: 1.4%/y Aspirin: 1.2%/y
ARISTOTLE[26] Phase III	Nonvalvular atrial fibrillation	5 mg BID	Warfarin (INR 2-3)	Median follow-up 1.8 y	Stroke or systemic embolism Apixaban: 1.3%/y * Warfarin: 1.6%/y	Apixaban: 2.1%/y * Warfarin: 3.1%/y
APPRAISE[27] Phase II	Secondary prevention after ACS	5Y20 mg/d	Placebo	26 wk	CV Death, MI, revascularization and Stroke 2.5 mg BID: 7.6% 10 mg/d: 6.0% Placebo: 8.7%	2.5 mg BID: 0.8% 10 mg/d: 0% 10 mg BID: 2.9% † 20 mg/d: 4.1% † Placebo: 0%
APPRAISE-2[28] Phase III	Secondary prevention after ACS	5 mg BID	Placebo	Median follow-up 241 d	CV Death, MI, and stroke Apixaban: 7.5% Placebo: 7.9%	Major Bleeding Apixaban: 1.3% † Placebo: 0.5%
ADVANCE1[29] Phase III	VTE prevention after TKR	2.5 mg BID	Enoxaparin 30 mg BID	12 d	VTE and all-cause mortality Apixaban: 9% Enoxaparin: 8.8%	Apixaban: 0.7% * Enoxaparin: 1.4%
ADVANCE-2[30] Phase III	VTE prevention after TKR	2.5 mg BID	Enoxaparin 40 mg/d	12 d	VTE and all-cause mortality Apixaban: 15% * Enoxaparin: 24%	Apixaban: 0.6% Enoxaparin: 0.9%
ADVANCE-3[52] Phase III	VTE prevention after THR	2.5 mg BID	Enoxaparin 40 mg/d	35 d	VTE and all-cause mortality Apixaban: 1.4% * Enoxaparin: 3.9%	Apixaban: 0.8% Enoxaparin: 0.7%
Botticelli DVT[53] Phase II	Acute VTE treatment	5 mg or 10 mg BID, 20 mg/d	Enoxaparin/warfarin	84Y91 d	VTE and increased thrombotic burden: 5 mg BID: 6% 10 mg BID: 5.6% 20 mg/d: 2.6% Warfarin: 4.2%	5 mg BID: 0.7% 10 mg BID: 0% 20 mg/d: 1.6% Warfarin: 0%
Metastatic cancer[54] Phase II	VTE prevention metastatic cancer	5Y20 mg	Placebo	12 wk	Symptomatic VTE Apixaban: 0% Placebo: 10%	5 mg: 0% 10 mg: 0% 20 mg: 6% Placebo: 3%

ACS, acute coronary syndrome; MI, myocardial infarction; THR, total hip replacement; TKR, total knee replacement.

*Statistically significant superiority demonstrated over comparator.

†Statistically significant inferiority demonstrated over comparator.

TABLE 5

Potential Useful Medications for Bleeding While on New Anticoagulants

Name	Agent Category	Clotting Factors in Product	Available in United States?
Tranexamic acid	Antifibrinolytic	None	Yes
? Aminoacaproic acid	Antifibrinolytic	None	Yes
NovoSeven	Activated factor VII	Activated VII	Yes
Cofact	4-Factor PCC	Nonactivated II, VII, IX, X	No
Beriplex, Octaplex	4-Factor PCC	Nonactivated II, VII, IX, X, Protein C and S	No
Profilnine, Bebulin	3-Factor PCC	Nonactivated II, IX, X, small amounts VII	Yes
Feiba	Activated PCC	Activated VII, nonactivated II, IX, X	Yes

TABLE 6

Timing of Discontinuation of New Oral Anticoagulants Before Standard Risk Procedures

Creatinine Clearance	Dabigatran	Rivaroxaban	Apixaban
>50 mL/min	24 h	24 h	24-36 h
30-50 mL/min	48 h	48 h	48 h
<30 mL/min	5 d		

Additional duration of discontinuation may be needed for high-risk procedures.[3,13,42]