CHAPTER **10**

NEW ORAL ANTICOAGULANTS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN THE FOOT AND ANKLE

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INTRODUCTION

Venous thromboembolism (VTE) is a common cause of morbidity and mortality. Each year in the US there are approximately 900,000 VTE events and 300,000 deaths as a result of VTEs. The cost of managing VTE is estimated to be as much as $1.5 billion annually (1, 2). For more than 50 years, the only available oral anticoagulant for long-term VTE treatment has been the vitamin K antagonists (Warfarin/Coumadin). However, these agents require bridging, have a narrow therapeutic range, require weekly monitoring, and have several other drawbacks. Over the last several years there have been advancements in the development of new oral anticoagulant medications (NOACs). These drugs originally gained approval for stroke prevention in atrial fibrillation, but have since gained approval for treatment or prophylaxis of VTEs. Vitamin K antagonists exert their effects on the coagulation through the inhibition of Factors II, VII, IX, and X. These new oral drugs prevent VTE by targeting Factor Xa or through direct thrombin inhibition (Figure 1). In the US there are currently 3 such drugs available: 2 Factor Xa inhibitors and one direct thrombin inhibitor.

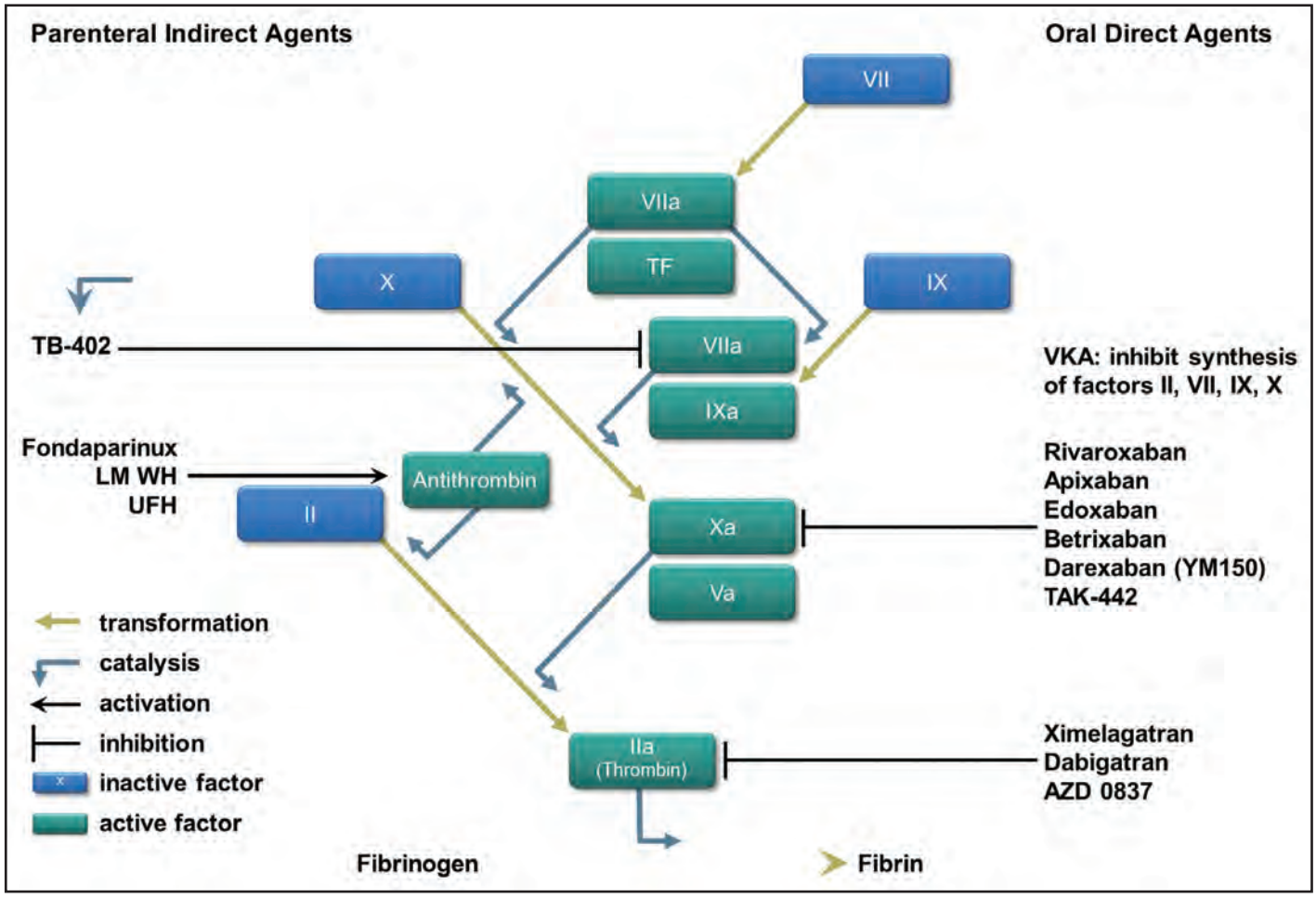

Figure 1. Targets for anticoagulants in use and development as thromboprophylaxis after total knee arthroplasty (15).

FACTOR XA INHIBITORS

Rivaroxaban (Xarelto, Janssen Pharmaceuticals)

Rivaroxaban is an oral, direct-acting, reversibly selective inhibitor of Factor Xa. It is approved by the Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for reduction of risk of recurrence of DVT and PE, and prophylaxis of DVT, which may lead to PE in patients undergoing knee and hip replacement surgery (3). Rivaroxaban has a rapid onset of action and its pharmacokinetics and pharmacodynamics are dose-proportional. In young, healthy patients elimination half-life at a steady state is 5 to 9 hours and can be up to 10 hours in elderly patients. Its absorption from the gastrointestinal tract is not affected by food. It is eliminated via a dual mode with one-third of the active drug excreted renally in an unchanged form, while the remaining two-thirds undergoes hepatic metabolism. The drug should be avoided in patients with severely impaired renal function (creatinine clearance < 30ml/min) (3).

The drug undergoes metabolism via cytochrome isoform CYP3A4. Therefore, the drug is contraindicated with concomitant therapy with potent CYP3A4 inhibitors, such as protease inhibitors, azole antifungals, and macrolide antibiotics. It also interacts with potent inhibitors of P-glycoprotein (p-gp) and is contraindicated with drugs like quinidine. Strong inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) should be avoided because they decrease exposure to the drug and increase risk of VTE and stroke. The most common adverse reaction with rivaroxaban is bleeding (3).

When used for VTE prophylaxis following hip and knee replacement surgery, the recommended dose is 10 mg taken orally with or without food. The initial dose should be given at least 6 to 10 hours after surgery once hemostasis has been established. Duration of treatment following hip replacement surgery is 35 days, and treatment duration for knee replacement is 12 days. There are no recommendations for treatment duration outside of hip and knee replacement surgery. If the drug must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped 24 hours prior to the procedure to reduce the risk of bleeding (3).

The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD 1) trial compared the efficacy and safety of 10 mg of oral rivaroxaban once daily initiated postoperatively, to 40 mg of enoxaparin subcutaneous once daily initiated preoperatively for VTE prevention in 4,541 patients undergoing total hip arthroplasty. The primary efficacy outcome occurred in 1.1% of the patients receiving rivaroxaban compared to 3.7% in those receiving enoxaparin, an absolute risk reduction of 2.6% ($P < 0.001$). Major bleeding events occurred in 0.3% of the rivaroxaban group and in 0.1% of the patients in the enoxaparin group ($P = 0.18$) (4).

In the RECORD 2 trial extended duration rivaroxaban (31-39 days) was compared to short-term enoxaparin (10-14 days) for total hip arthroplasty in 2,509 patients. Rivaroxaban was associated with a lower risk of VTE and all cause mortality (2%) versus enoxaparin (9.3%) an absolute risk reduction of 7.3% ($P < 0.0001$). Major bleeding events were very similar, with 6.6% in the rivaroxaban group and 5.5% in the enoxaparin group ($P = 0.25$) (5).

The RECORD 3 trial compared 2,531 knee replacement patients receiving the same dose of either rivaroxaban or enoxaparin. Rivaroxaban was again found to be superior to enoxaparin for VTE prevention and all-cause mortality 13-17 days postoperative, 9.6% versus 18.9%, an absolute risk reduction of 9.2% ($P < 0.001$). Major bleeding events were again very similar, with 0.6% in the rivaroxaban group and 0.5% in the enoxaparin group (6).

The RECORD 4 study compared 3,148 knee replacement patients who were randomized to once daily rivaroxaban, 2x 30 mg enoxaparin, or 40 mg of enoxaparin, which was the dose used in previous RECORD studies. Rivaroxaban again showed a significant reduction in primary outcome events (6.9% versus 10.1) with an absolute risk reduction of 3.19% ($P = 0.0118$), and comparable major bleeding events (rivaroxaban 0.7% versus enoxaparin 0.3%, ($P = 0.1096$). The RECORD trials showed the comparable safety and superior efficacy of rivaroxaban compared with enoxaparin for VTE prophylaxis after hip and knee replacement surgery (7).

Apixaban (Eliquis, Bristol-Myers Squibb)

Apixaban, like rivaroxaban, is an oral, direct-acting, selective inhibitor of Factor Xa. It is FDA approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, prophylaxis of DVT following hip and knee replacement surgery, treatment of DVT/PE, and reduction in risk of recurrence. Apixaban has a rapid absorption with a half-life of approximately 12 hours. Food intake does not affect the drug's absorption. Apixaban is eliminated in both urine and feces with biliary and direct intestinal excretion accounting for 75% and renal 25%. The drug should be avoided in patients with severely impaired renal function (creatine clearance < 30ml/min). Like rivaroxaban, apixaban undergoes metabolism via cytochrome isoform CYP3A4 and is contraindicated with concomitant therapy with potent CYP3A4 and P-gp inhibitors. Strong inducers of CYP3A4 and P-gp should also be avoided due to increased thrombus risk. The most common adverse reaction with Apixaban is bleeding (8).

When used for VTE prophylaxis following hip and knee replacement surgery, the recommended dose is 2.5 mg taken orally twice daily. The initial dose should be given at least 12 to 24 hours after surgery once hemostasis has been established. Duration of treatment following hip replacement surgery is 35 days, and treatment duration for knee replacement is 12 days. There are no recommendations for treatment duration outside of hip and knee replacement surgery. If the drug must be discontinued to reduce the risk of bleeding with surgical or other procedures, apixaban should be stopped 48 hours prior to any elective surgery or procedure with a moderate to high risk of bleeding, and 24 hours prior to any elective surgery or procedure with a low risk of bleeding (8)

The Apixaban for the Prevention of Thrombosis-related Events 1 study (ADVANCE) compared 1,599 patients taking 2.5 mg apixaban twice a day following knee replacement with 1,596 patients who received 30 mg of enoxaparin twice a day. The primary efficacy outcome was similar between the two groups with 9.0% in the apixaban group and 8.8% in the enoxaparin group. However, the apixaban group was had a significant reduction in the incidence of major and clinically relevant nonmajor bleeding episodes with 2.9% in the apixaban group and 4.3% in the enoxaparin group ($P < 0.05$) (9).

In the ADVANCE 2 trial 3,057 patients received the same apixaban dose or 40 mg of enoxaparin after knee replacement surgery. There was a significant reduction in the incidence of total VTE in the apixaban group 15.1% versus enoxaparin 24.4%, absolute risk reduction of 9.3% ($P < 0.0001$). There was a nonsignificant reduction in bleeding with apixaban 4% versus enoxaparin 5% ($P = 0.09$) (10).

The ADVANCE 3 trial compared 5,407 patients undergoing hip arthroplasty who received either 2.5 mg apixaban twice daily or 40 mg of enoxaparin 40 mg once daily for 5 weeks postoperative. The primary efficacy outcome for apixaban was 1.4% compared to 3.9% for enoxaparin, relative risk 0.36 ($P < 0.001$). The incidence of major and clinically relevant nonmajor bleeding was 4.8% with apixaban and 5.0 with enoxaparin (11).

DIRECT THROMBIN INHIBITORS

Dabigatran Etexilate (Pradaxa, Boehringer Ingeleheim Pharmaceuticals)

Dabigatran etexilate is an orally active competitive, direct thrombin inhibitor. It reversibly inhibits both free and fibrin-bound thrombin, thereby preventing thrombus formation. It is a pro-drug, which is rapidly converted to dabigatran,

Level of Urgency	Warfarin	Dabigatran	Rivaroxaban or Apixaban
No rush (>24 hr)	Withhold warfarin and consider oral phytonadione, with dose based on INR	Withhold drug and monitor clinical status and pertinent laboratory tests	Withhold drug and monitor clinical status and pertinent laboratory tests
Expedited (1-24 hr)	Withhold drug and give oral phytonadione (1-5 mg) or low-dose i.v. phytonadione (0.25-5mg),with dose based on initial INR and postreversal INR (checked 24 hr after dose)	Withhold drug, give activated charcoal if last dose was taken within past 2 hr, and use prolonged hemodialysis (>2 hr)	Withhold drug and give activated charcoal if last dose was taken within past 2 hr and repeat 6 hr after the last dose
Emergent (<1 hr)	Withhold drug, consider high-dose i.v. phytonadione (depending on anticipated need to restart warfarin), and consider clotting factor supplement (listed in order of preference): • PCC4 • Build PCC4 with PC3 plus rFVIIa • aPCC • PC3 • rFVIIa • FFP	Withhold drug, give activated charcoal if last dose was taken within past 2 hr, use prolonged hemodialysis (>2 hr),and consider clotting factor supplement (listed in order of preference): • aPCC • PCC4 • Build PCC4 with PC3 plus rFVIIa	Withhold drug, give activated charcoal if last dose was taken within past 2 hr and repeat 6 hr after the last dose, and consider clotting factor supplement (listed in order of preference): • PCC4 • aPCC • Build PCC4 with PC3 plus rFVIIa • PC3

Figure 2. Therapeutic interventions for reversal of oral anticoagulants by urgency (16).

its active moiety by esterase-mediated hydrolysis in both the plasma and liver. It is FDA approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treatment of DVT/PE in patients treated with parenteral anticoagulants for 5-10 days, and reduction in risk of DVT/PE recurrence in patients who have previously been treated (12).

Its oral bioavailability is much lower than the other 2 NOAC drugs at 6-7%. Its half-life is also the longest of all the drugs at 14-17 hours. Time to peak plasma levels of dabigatran etexilate are prolonged by approximately 2 hours without significant effects on overall exposure when administered with food. Dabigatran is primarily excreted unchanged in the kidneys (80%). Plasma levels are increased in patients with renal insufficiency therefore half the dose should be given in patients with moderate renal impairment (creatine clearance 30-50 ml/min). Unlike the Factor Xa inhibitors, dabigatran is not metabolized by cytochrome P450 isoenzymes. However, the pro-drug Dabigatran etexilate is a substrate of P-gp. Therefore, inhibitors of P-gp like verapamil, amiodarone, and quinidine will increase plasma levels of dabigatran requiring dose adjustments. Inducers of P-gp like rifampin reduce exposure to the drug and should generally be avoided (12).

Dabigatran does not have FDA approval for VTE prophylaxis after hip and knee replacement surgery in the US. However, in the European Union (EU) the recommended dose is 220 mg taken orally once daily taken as 2 capsules of 110 mg when used for VTE prophylaxis following hip and knee replacement surgery. Treatment should be initiated 1-4 hours after surgery with a single 110 mg capsule and continuing with 2 capsules once daily thereafter for 10 days following knee replacement, and 28-35 days for hip replacement. There are no recommendations for treatment duration outside of hip and knee replacement surgery. If the drug must be discontinued to reduce the risk of bleeding with surgical or other procedures, dabigatran should be discontinued 1-2 days before surgery (creatine clearance >50 ml/min) or 3-5 days (creatine clearance <50 ml/min), consider longer times in patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port (12).

The RE-MODEL trial was a randomized, double-blind study that included 2,076 patients who underwent total knee replacement. It compared dabigatran 150 mg or 220 mg once daily for 6-10 days to the EU enoxaparin dose of 40 mg subcutaneous once daily. The efficacy was found to be similar (150 mg dabigatran 40.5%, 220 mg dabigatran 36.4%, and enoxaparin 37.7%). The incidence of major bleeding did not differ significantly between them 1.3%, 1.5%, and 1.3% respectively (13).

The RE-MOBILIZE trial looked at 1,896 patients undergoing total knee replacement with patients receiving dabigatran 150 mg or 220 mg once daily or 30 mg of enoxaparin for 12-15 days. Dabigatran was found to be statistically inferior to 30 mg of enoxaparin (enoxaparin 25%, 150 mg dabigatran 34% $P < 0.001$, 220 mg dabigatran 31% $P = 0.02$). There were no significant differences in major bleeding 1.4%, 0.6%, and 0.6% respectively (14).

REVERSAL

There are no specific reversal agents available for the NOACs. The literature is limited in terms of reversal of these drugs. Supportive measure should be given including fluids and packed red blood cells. Figure 2 gives the clinical practice guidelines for therapeutic interventions for reversal of oral anticoagulants by urgency. Specific reversal agents are currently in development. A recombinant modified human Factor Xa and antibody fragment of dabigatran are currently in phase 3 trials (16).

CONCLUSION

Current anticoagulants have limitations that are obviated by the NOACs. The efficacy and safety of NOACs are comparable to those of existing therapies. Although there are no current therapeutic guidelines for use in the foot and ankle, these new drugs could potentially replace vitamin K antagonists for VTE prophylaxis. As these drugs become commonplace in clinical practice, it is imperative that we as physicians be aware of their pharmacologic properties.

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