

WJO 5th Anniversary Special Issues (4): Hip**New oral pharmacotherapeutic agents for venous thromboprophylaxis after total hip arthroplasty**

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Abstract

Patients undergoing total hip arthroplasty (THA) are at high risk for developing venous thromboembolism and, therefore, require short term prophylaxis with anti-thrombotic agents. Recently, target specific oral anticoagulants (TSOA) including the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have been approved for THA thromboprophylaxis in various countries. The TSOAs provide a rapid acting, oral alternative to parenteral agents including low-molecular weight heparins (LMWH) and fondaparinux; and compared to warfarin, they do not require routine laboratory monitoring and possess much fewer drug-drug interactions. Based on phase III clinical studies, TSOAs have established themselves

as an effective and safe option for thromboprophylaxis after THA compared to LMWH, particularly enoxaparin, but require additional evaluation in specific populations such as the renally impaired or elderly. The ability to monitor and reverse these TSOAs in the case of bleeding complications or suspected sub- or supra-therapeutic anticoagulation is of importance, but remains investigational. This review will focus on the drug-specific characteristics, efficacy, safety, and economic impact of the TSOAs for thromboprophylaxis following THA, as well as the aspects of therapeutic monitoring and anticoagulation reversal in the event of bleeding complications or a need for urgent reversal.

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Key words: Oral; Thromboprophylaxis; Venous thromboembolism; Hip; Arthroplasty

Core tip: This review focuses on the drug-specific characteristics, efficacy, safety, and economic impact of the target specific oral anticoagulants including dabigatran, rivaroxaban, apixaban, and edoxaban for thromboprophylaxis following total hip arthroplasty, as well as the aspects of therapeutic monitoring and anticoagulation reversal in the event of bleeding complications or a need for urgent reversal.

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INTRODUCTION

Patients undergoing major orthopedic surgery including

total hip arthroplasty (THA) are at increased risk for developing venous thromboembolism (VTE) that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Methods of mechanical and/or pharmacologic thromboprophylaxis have greatly reduced the VTE risk. The historical risk of symptomatic VTE following orthopedic surgery without thromboprophylaxis ranged from 15%-30% but more recent analysis suggest a cumulative VTE rate of 4.3% in the 35 d following major orthopedic surgery including THA, hip fracture repair, and total knee arthroplasty (TKA)^[1]. In contrast, the rate of symptomatic VTE in the presence of thromboprophylaxis prior to hospital discharge has recently been determined to be as low as 0.53% following orthopedic surgery^[2]. The rate of VTE is increased when followed up to 35 d post-surgery with a 1%-3% incidence of symptomatic DVT and 0.2%-1.1% incidence of PE after orthopedic surgery^[1]. The 90-d symptomatic VTE rate after THA using thromboprophylaxis for the indicated duration ranges from 2.4%-2.8%^[1]. Also, pharmacologic thromboprophylaxis was significantly associated with a decrease in 90-d mortality in a recent analysis of over 400000 THA patients from the National Joint Registry for England and Wales^[3].

THROMBOPROPHYLAXIS FOR THA

The value of pharmacologic thromboprophylaxis in THA has been recognized in evidenced-based treatment guidelines by several groups including the American College of Chest Physicians (ACCP)^[1], the American Academy of Orthopedic Surgeons (AAOS)^[4], and the National Institute for Health and Clinical Excellence (NICE)^[5,6]. Low-molecular weight heparins (LMWHs), fondaparinux, warfarin, and acetylsalicylic acid (aspirin) are recommended as options for routine thromboprophylaxis, with a LMWH currently the most widely used agent worldwide^[7]. However, disadvantages that may lead to patient nonadherence and consequently an increased risk of thrombotic events are associated with these agents. LMWHs and fondaparinux are parenteral agents that require daily injections by the patient and are costly. Warfarin takes several days to weeks to achieve stable therapeutic effects, thereby requiring a patient to comply with frequent laboratory monitoring. Moreover, whether the efficacy of a simple oral aspirin regimen is comparable to that of the other agents remains controversial^[8-11].

The benefit of pharmacologic thromboprophylaxis must be weighed against an increased risk of major bleeding estimated to be as high as 5.4% compared to 1.5% without thromboprophylaxis in orthopedic surgery patients^[1,12,13]. Bleeding at the surgical site and neuraxial hematoma are of particular concern^[12]. The incidence of surgical site bleeding has been found to be 1%-2% in patients receiving anticoagulation following orthopedic surgery, an event that increases pain, inflammation, the risk of infection, and readmission^[14]. Although rare, the risk of neuraxial hematomas is increased with the use of anticoagulants and can lead to severe neurological com-

plications and/or death^[15].

Thromboprophylaxis is recommended to be continued up to 35 d following THA, making both outpatient medication compliance and the risk of anticoagulant adverse effects areas of concern^[1]. The need for an improved agent for thromboprophylaxis for THA as well as other thrombotic disorders has driven the development of rapid acting, effective and safe oral anticoagulants with predictable pharmacokinetics and pharmacodynamics that alleviate the need for frequent laboratory monitoring. New oral anticoagulant agents (NOACs) include agents that target the inhibition of one of two critical elements of the clotting cascade, factor II (thrombin) and factor Xa (FXa). Since the agents have now been available for a period of time, they are also termed target-specific oral anticoagulants (TSOAs). Regardless, the class of new oral anticoagulant agents presently includes the direct thrombin inhibitor dabigatran and the FXa inhibitors rivaroxaban, apixaban, and edoxaban; each agent has been approved in various countries for primary prevention of VTE following THA.

This review will focus on the drug-specific characteristics, efficacy, safety, and economic impact of the TSOAs for thromboprophylaxis following THA. Also, aspects related to therapeutic monitoring of suspected sub- or supra-therapeutic anticoagulation and the issue of anticoagulation reversal in the event of bleeding complications or a need for urgent reversal will be discussed.

OVERVIEW OF TSOAS

Each of the TSOAs has, or is being studied for therapeutic indications beyond thromboprophylaxis for THA. Dabigatran was originally approved in the United States by the Food and Drug Administration (FDA) in 2010 for the prevention of stroke in patients with non-valvular atrial fibrillation and again in 2014 for the treatment and secondary prevention of VTE^[16]. It currently is approved in Europe and Canada, and used off-label in the United States for thromboprophylaxis of orthopedic surgery including THA^[17]. Rivaroxaban is approved in the United States for thromboprophylaxis in orthopedic surgery, as well as treatment of VTE and for stroke prevention in patients with non-valvular atrial fibrillation^[18,19]. Apixaban is indicated for thromboprophylaxis after orthopedic surgery by the European Medicine Agency (EMA) and more recently the FDA in 2014, and for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation by the FDA and EMA^[20,21]. Edoxaban is approved in Japan for VTE thromboprophylaxis in major orthopedic surgery, and is under current investigation for other indications in several countries^[22-25]. Betrixaban is a fourth FXa inhibitor that is currently under investigation for orthopedic thromboprophylaxis^[26]. It is important to note that the recommended dosage for each of the drugs varies according to the treatment indication and that the recommended dosage for orthopedic thromboprophylaxis is lower than that used for VTE treatment or stroke prophylaxis in patients with atrial fibrillation.

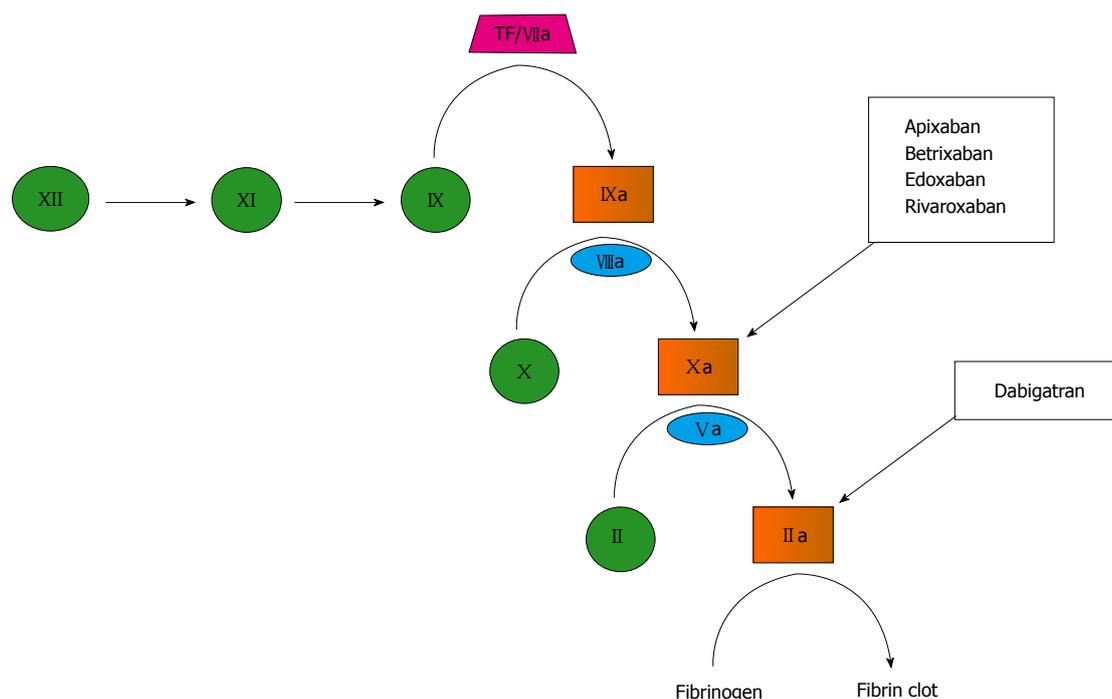


Figure 1 Coagulation cascade and site of target specific oral anticoagulants action.

Dabigatran directly binds to the active catalytic site and reversibly inhibits both free and clot-bound thrombin. Inhibition of thrombin disables conversion of fibrinogen to fibrin, inhibits activation of factors V, VIII, XI (factors that further promote thrombin generation), and inhibits factor XIII that promotes clot stabilization^[26-28]. Rivaroxaban, apixaban, and edoxaban directly inhibit both free and clot-bound FXa, as well as prothrombinase activity. Inhibition of FXa in turn prevents the formation of thrombin. Platelet aggregation is directly inhibited by dabigatran and indirectly inhibited by the FXa inhibitors due to their effects to reduce thrombin production^[29-31] (Figure 1).

Pharmacokinetics and pharmacodynamics of the TSOAs

Because dabigatran is poorly absorbed after oral administration, the drug product is formulated as a pro-drug dabigatran etexilate that is rapidly hydrolyzed to its active form^[16]. Dabigatran undergoes hepatic glucuronidation to form 4 active acyl glucuronides, each accounting for < 10% of total dabigatran in plasma. Peak plasma concentration is seen in 1 h in a fasting state but prolonged up to 3 h if administered with a meal high in fat. Once absorbed, dabigatran is only 35% plasma protein bound. Dabigatran primarily undergoes renal elimination and approximately 80% is excreted as unchanged active drug. As with all TSOAs, dabigatran's half-life of 12-17 h in healthy adults is much shorter than that seen with warfarin^[32-35] (Table 1).

As would be expected, the half-life of dabigatran is prolonged to approximately 27-28 h in the presence of significant renal impairment, defined as a creatinine clearance (CrCl) of < 30 mL/min^[36]. A dose reduction from

220 to 150 mg daily has been recommended for patients with moderate renal impairment (CrCl 30-50 mL/min) based on a post hoc analysis of phase III clinical studies in orthopedic patients^[37]. It has also been recommended to avoid use of dabigatran following THA in the case of severe renal impairment (CrCl < 30 mL/min), although a reduced dose of 150 mg daily in two divided doses down to a CrCl of 15 mL/min has been approved for other therapeutic indications based on pharmacokinetic analysis^[38]. Additionally, due to its lack of CYP450 involvement, no dosing adjustment is necessary in the case of hepatic dysfunction^[16].

The pharmacokinetics of rivaroxaban have been described for the THA thromboprophylaxis dosage of 10 mg once daily^[18,19,39,40]. The drug is rapidly and nearly completely absorbed (80%-100%) without regard to food, with a peak concentration seen in 2-4 h. Unlike dabigatran, the drug is almost entirely protein bound (92%-95%). Approximately one-third of a rivaroxaban dose is eliminated unchanged through the kidneys while the remaining parent drug is metabolized to inactive metabolites by cytochrome P-450 (CYP450) isoenzymes CYP3A4/5, and CYP2J2. A half-life of 5-9 h in healthy young adults (age 25-45 years) is prolonged to approximately 11-13 h in the elderly population^[18,19,27].

As noted, rivaroxaban concentrations may be increased in patients with moderate to severe renal impairment. Based on outcomes from phase III studies, no dosing adjustment is required in patients with moderate renal impairment (CrCl 30-50 mL/min). In the case of severe renal impairment, rivaroxaban has been considered contraindicated in the United States at a CrCl < 30, and in Europe at a CrCl < 15^[18,19]. Rivaroxaban dose

Table 1 Target specific oral anticoagulant pharmacokinetics

	Dabigatran etexilate ^[17,32-36]	Rivaroxaban ^[19,27,39,40]	Apixaban ^[21,27,41,42]	Edoxaban ^[43-45]
Half Life (t _{1/2})	(1) Healthy subjects: 12-15 h (2) Mild renal impairment (50-80 mL/min): 15 h (3) Moderate renal impairment (30-50 mL/min): 18 h (4) Severe renal impairment (15-30 mL/min): 27 h	(1) Healthy subjects: - 5-9 h (2) Elderly: 11-19 h (3) Mild to moderate hepatic impairment: 10.1-10.4 h (4) Mild renal impairment (50-79 mL/min): 8.7 h (5) Moderate renal impairment (30-49 mL/min): 9 h (6) Severe renal impairment (15-29 mL/min): 9.5 h	(1) 2.5 mg: 6.8 h (2) 5 mg: 15.2 h (3) 10 mg: 11.1 h	8.75-10.4 h
Distribution	Vd: 50-70 L	Vd: 50 L	Vd: 21 L	Vd: > 300 L
Protein binding	35%	92%-95%	87%	40%-59%
Metabolism	(1) Hepatic: dabigatran etexilate is hydrolyzed to dabigatran (active form). (2) Dabigatran undergoes hepatic glucouronidation to 4 active acyl glucuronides, each accounting for < 10% of total dabigatran in plasma.	Hepatic: oxidative metabolism <i>via</i> CYP3A4/5 and CYP2J2	Hepatic: mainly <i>via</i> CYP3A4/5 with minor contribution from CYP1A2, CYP2C8/9/19, and CYP2J2	Hepatic: minimal hepatic contribution from CYP3A4
Bioavailability	3%-7%	Dose dependent (absolute bioavailability) (1) 10 mg 80%-100% in fasted state (2) 20 mg approximately 66% in fasted state	50%	62%
Onset (T _{max})	1-6 h (1) Healthy subjects in fasted state-1 h (2) Healthy subjects following high fat meal-3 h (3) Subjects undergoing elective hip surgery-6 h	2-4 h	2.5 mg: 1.5 h 5 mg: 3.3 h 10 mg: 3-4 h	1-2 h
Excretion	80% renal clearance	(1) 66% renal clearance (36% unchanged and 30% as inactive metabolite); (2) 28% fecal excretion (7% unchanged and 21% as inactive metabolite)	(1) 27% renal clearance unchanged (2) 25% fecal excretion unchanged	49% renal clearance

reduction is approved for use in patients with atrial fibrillation and who have a CrCl 15-50 mL/min; the drug is not recommended for any indication if the CrCl < 15 mL/min^[18,19,39]. Additionally, rivaroxaban use is not recommended for use in the presence of moderate to severe hepatic dysfunction or hepatic disease that is associated with coagulopathy^[40].

While it might be expected that apixaban pharmacokinetics are similar to those of rivaroxaban, such is not entirely the case. The drug is rapidly absorbed with a peak effect in 3-4 h; however, only 50% of a dose reaches circulation while the remainder is excreted unchanged in the feces. The drug is approximately 87% protein bound and like rivaroxaban, is eliminated by both hepatic and renal mechanisms. Apixaban is primarily metabolized *via* CYP3A4 with minor contribution by other CYP enzymes and there are no active circulating metabolites.

Because only 25% of a dose is eliminated unchanged through the kidneys, renal impairment does not significantly prolong the average half-life of 8-15 h^[27,41,42]. However, due to limited clinical evidence, apixaban should be used with caution in patients with severe renal impairment (CrCl 15-30 mL/min) and is not recommended in those with a CrCl < 15 mL/min or undergoing dialysis. No apixaban dosing adjustments are required for patients with moderate hepatic impairment although the drug is not recommended for patients with severe hepatic dysfunction^[21].

Edoxaban is rapidly absorbed with 60% bioavailability, and reaches peak plasma concentrations in 1-2

h^[43,44]. Most of an edoxaban dose is excreted unchanged in either the urine or feces. Edoxaban appears to be eliminated through a multitude of pathways with negligible contribution from CYP450 isoenzymes^[44]. Roughly half of edoxaban present in plasma is eliminated by the kidneys, causing prolonged drug exposure in those with renal dysfunction. In healthy individuals, repeated doses of edoxaban demonstrate a half-life of 9-10 h and would likely be prolonged with renal impairment, although to what extent has not been fully delineated^[44,45].

Drug interactions with TSOAs

Drug interactions with TSOAs can occur when another drug alters the pharmacokinetics of the anticoagulant or as a result of additive pharmacodynamic effects on coagulation. Either type of drug interaction can affect the predictable effects on coagulation of the newer agent. Pharmacokinetic-based interactions may lead to decreased or increased exposure of the TSOA, resulting in greater risk of thrombosis or bleeding, respectively. Pharmacodynamic-based interactions are of concern because of an enhanced bleeding risk. Because of the lower dosage and shorter duration of therapy of the TSOA used for THA thromboprophylaxis, drug interactions contributing to an increased bleeding risk may be less important compared to other patient populations. On the other hand, drug interactions resulting in a diminished TSOA effect almost certainly represent a clinically significant concern.

The permeability glycoprotein (P-gp) is an efflux

Table 2 Effects on target specific oral anticoagulants plasma concentrations from drug-drug interactions and dosing recommendations

	Drug interaction <i>via</i>	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+ 12%-180% (take simultaneously and reduce dose)	Minor effect (use caution with CrCl 15-50 mL/min)	No data yet	+ 53% (SR verapamil) (reduce dose by 50%)
Diltiazem	P-gp inhibition	No effect	Minor effect (use caution with CrCl 15-50 mL/min)	+ 40%	No data yet
Quinidine	P-gp inhibition	+ 50%	+ 50%	No data yet	+ 80% (reduce dose by 50%)
Amiodarone	P-gp inhibition	+ 12%-60%	Minor effect (use caution with CrCl 15-50 mL/min)	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+ 70%-100% (75 mg BID)	No data yet	No data yet	+ 85% (reduce dose by 50%)
Azole antifungals (1) Voriconazole (2) Ketoconazole (3) Itraconazole (4) Posaconazole	Strong P-gp and CYP3A4 inhibition	+ 140%-150% (75 mg BID)	Up to + 160%	+ 100%	No data yet
Fluconazole	Moderate CYP3A4 inhibition	No data yet	+ 42%	No data yet	No data yet
Clarithromycin	Strong P-gp and CYP3A4 inhibition	-0.05	+ 30%-54%	No data yet	No data yet
Erythromycin	Strong P-gp and CYP3A4 inhibition	No data yet	Up to + 153%	Strong increase	No data yet
HIV Protease Inhibitors	Strong P-gp and CYP3A4 induction	- 66%	Up to - 50%	- 54%	- 35%
Rifampin					
St. John's Wort					
Carbamazepine					
Phenytoin					
Phenobarbital					

Table adapted from EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation^[46]. Grey boxes indicate drug contraindicated or not recommended. AUC: Area under the curve; TSOA: Target specific oral anticoagulant; P-gp: Permeability glycoprotein; BID: Twice daily.

transporter protein that is primarily expressed in the small intestines, hepatocytes, and the renal proximal tubules of the kidneys. P-gp mediates the transportation of many medications and endogenous compounds across the cell membranes. Drugs can either induce or inhibit the action of the P-gp transporter, resulting in drug-drug interactions. Regarding some TSOAs, inducing P-gp can lead to reduced plasma drug concentrations and a greater risk of thrombosis, while inhibiting P-gp will elevate serum drug concentration and increase the risk of bleeding. Alteration of one or more of the CYP450 isoenzymes is another common source of drug-drug interaction, since many medications have the potential for either inducing or inhibiting CYP450 isoenzymes, thus affecting the metabolism of certain other drugs^[42].

Dabigatran is a substrate for the P-gp efflux transporter that is responsible for most of its clinically significant drug interactions; the drug is not a substrate for any CYP450 isoenzymes. Only moderate (*e.g.*, amiodarone, quinidine, and verapamil) and strong (*e.g.*, cyclosporine, dronedarone, itraconazole, systemic ketoconazole, and tacrolimus) P-gp inhibitors impact the serum concentration of dabigatran and potentiate its effects. Dabigatran use should be avoided in patients requiring the use of strong P-gp inhibitors. Renal dysfunction, in addition to concomitant use of a P-gp inhibitor, can greatly increase the exposure to dabigatran. Consequently, a reduced dose of dabigatran has been recommended if co-administered with moderate P-gp inhibitors such as amiodarone or

quinidine (each reduced to 150 mg daily), or verapamil (reduced to 75 mg daily) in a patient with a CrCl 30-50 mL/min. Concomitant use of dabigatran and moderate or strong P-gp inhibitors should be avoided in patients with severe renal dysfunction (CrCl < 30 mL/min). Similarly, dabigatran co-administration with all moderate to strong inducers of P-gp should be avoided, as they can decrease serum dabigatran concentrations and potentially decrease efficacy^[17,42,46,47] (Table 2).

Both rivaroxaban and apixaban are metabolized via CYP450 isoenzymes and also are substrates of the P-gp efflux transporter leading to several significant drug-drug interactions, particularly with agents that are strong inhibitors or inducers of both CYP3A4 and P-gp^[42,46]. Strong “combined” inhibitors of both CYP3A4 and P-gp (*e.g.*, ketoconazole, itraconazole, ritonavir, and conivaptan) can significantly increase rivaroxaban or apixaban concentrations. In contrast, strong inducers of both CYP3A4 and P-gp (*e.g.*, carbamazepine, phenytoin, rifampin, and St. John's wort) may decrease the serum concentration of rivaroxaban or apixaban. Therefore, co-administration of either of rivaroxaban or apixaban with strong combined CYP3A4 plus P-gp inhibitors or inducers should be avoided^[18]. It has been determined however, that inhibition of P-gp alone will cause only modest changes to the pharmacokinetic properties of rivaroxaban or apixaban^[42].

As is the case with other TSOAs, edoxaban is a substrate of P-gp. Both inducers and inhibitors of the P-gp

will influence the serum concentrations of edoxaban. Increased edoxaban exposure has been demonstrated with the co-administration of P-gp inhibitors verapamil, quinidine, and dronedarone. However, unlike other FXa inhibitors, there is minimal CYP enzyme involvement and drugs influencing CYP enzymes theoretically pose little risk of interacting with edoxaban^[1,2,42,48].

Regarding pharmacodynamic interactions resulting in an increased bleeding risk, there is a clear theoretical additive risk when a TSOA is concomitantly used with an antiplatelet agent, a nonsteroidal anti-inflammatory drug (NSAID), or another anticoagulant. While it is preferred to avoid or limit simultaneous use of a TSOA with any of these agents, many THA patients are taking antiplatelet agents for cardiovascular disease and approximately 50%-70% of orthopedic surgery patients received concurrent NSAID or aspirin therapy during the major clinical trials^[49-51].

Friedman *et al.*^[50] conducted a post-hoc analysis of major bleeding rates from pooled data of three major orthopedic thromboprophylaxis trials of dabigatran compared to enoxaparin; 42% of the 8135 patients studied had undergone THA. The investigators separately analyzed the bleeding rates for concomitant anticoagulant plus either aspirin (4.7%) or a NSAID (54.1%). Results demonstrated no significant difference in major bleeding risk when either dabigatran or enoxaparin was combined with either aspirin or a NSAID. A similar analysis by Eriksson *et al.*^[51] used rivaroxaban versus enoxaparin pooled data from phase III studies; 57% of the 12220 patients studied had undergone THA. Co-administration of the anticoagulant with either a NSAID or an antiplatelet agent occurred in 72.3% and 8.9% of patients, respectively. Rate ratios (RRs) for any bleeding event and for major bleeding were not significantly increased in patients with concomitant anticoagulant plus NSAID or antiplatelet drug use, and there was no difference between RRs for rivaroxaban compared to enoxaparin. Nevertheless, it is prudent to evaluate the signs and symptoms of blood loss frequently when concomitant use of a TSOA and an antiplatelet or NSAID is warranted^[1,16,18,20].

CLINICAL STUDIES OF TSOAS IN THA PATIENTS

Dabigatran in THA

Dabigatran was first evaluated in THA patients in the phase II studies Boehringer Ingelheim Study in ThROMbosis (BISTRO) I and BISTRO II. Results of the dose-ranging BISTRO I study^[52] demonstrated that an acceptable safety profile would be seen with dabigatran dosages of 12.5 to 300 mg daily after THA or TKA, but the study was not powered to determine efficacy. Investigators in the larger BISTRO II study^[53] determined that a dose dependent relationship existed for both dabigatran efficacy and safety, with significantly fewer VTE events at higher doses compared to enoxaparin 40 mg after THA or TKA, and a strong trend towards an increased rate of

major bleeding with the highest dabigatran dose (300 mg daily) *vs* enoxaparin ($P = 0.051$). Collectively, data from the BISTRO studies established dabigatran 150 mg and 220 mg daily as the two most effective thromboprophylaxis dosages, while maintaining a comparable safety profile to enoxaparin.

The extended thromboembolism prevention after hip surgery (RE-NOVATE)^[54] and RE-NOVATE II^[47] studies were randomized, double-blind, non-inferiority Phase III studies of 3494 and 2055 patients, respectively, designed to evaluate the efficacy and safety of dabigatran compared to enoxaparin for VTE prophylaxis after THA (Table 3). RE-NOVATE randomized patients to either dabigatran 150 mg or 220 mg given orally once daily, or enoxaparin 40 mg subcutaneously once daily. RE-NOVATE II focused solely on dabigatran 220 mg daily compared to enoxaparin. In each study, dabigatran was started 1-4 h after surgery at a half-dose then continued at its full dose daily beginning post-operative day 1. Enoxaparin was started the evening before surgery, and then continued once daily following surgery, although the investigators did allow for enoxaparin to be initiated post-operatively if consistent with local practice. Thromboprophylaxis was continued for either agent for 28-35 d. A primacy efficacy outcome of any VTE or all-cause mortality and a primary safety outcome of major bleeding during the treatment period were established. Both studies evaluated major VTE as defined by proximal DVT, non-fatal PE, or VTE-related death as a secondary outcome^[47,54].

The RE-NOVATE investigators found the incidence of primary efficacy outcome occurred in 8.6% (75/874) of dabigatran 150 mg, 6.0% (53/880) of dabigatran 220 mg, and 6.7% (60/897) of enoxaparin 40 mg patients, respectively. Both doses of dabigatran achieved non-inferiority ($P < 0.0001$) with no differences in the rates of major VTE for either dabigatran group compared to enoxaparin. Major and minor bleeding rates were also similar between all groups^[54].

RE-NOVATE II was focused solely on dabigatran 220 mg orally once daily compared to enoxaparin 40 mg subcutaneously daily. Results showed any VTE or death occurred in 7.7% (61/792) of dabigatran compared to 8.8% (69/785) of enoxaparin patients ($P = 0.43$), establishing non-inferiority with dabigatran. There was, however, a significant difference in the rate of major VTE between dabigatran and enoxaparin (2.2% *vs* 4.2%, $P = 0.03$)^[47].

Results of both RE-NOVATE and RE-NOVATE II studies demonstrated similar rates of major and minor bleeding between dabigatran and enoxaparin^[47,54]. A pooled analysis of phase III studies of orthopedic thromboprophylaxis (excluding RE-NOVATE II) found no differences in surgical site bleeding or wound infection although smaller independent investigations have since suggested a possible increased risk of post-operative wound complications with dabigatran compared to LMWH^[55,56]. No incidence of spinal hematoma was ob-

Table 3 Phase III clinical trials of target specific oral anticoagulants (target specific oral anticoagulants)

Clinical trial	TSOA regimen (duration)	Enoxaparin regimen (duration)	Composite of total venous thromboembolism and death		P-value, non-inferiority (superiority)	Major bleeding		P-value
			TSOA % (n/N)	Enoxaparin % (n/N)		TSOA % (n/N)	Enoxaparin % (n/N)	
RE-NOVATE ^[54] (N = 3494)	Dabigatran 220 mg daily (28-35 d)	40 mg daily (28-35 d)	220 mg; 3.1% (28/909)	6.0% (53/880)	< 0.0001 (n/a)	220 mg; 2.0% (23/1146)	1.6% (18/1154)	0.44
	Dabigatran 150 mg daily (28-35 d)		150 mg; 8.6% (75/874)		< 0.0001 (n/a)	150 mg; 1.3% (15/1163)		0.6
RE-NOVATE II ^[47] (N = 2055)	Dabigatran 220 mg daily (28-35 d)	40 mg daily (28-35 d)	7.7% (61/792)	8.8% (69/785)	< 0.0001 (0.43)	1.4% (14/1010)	0.9% (9/1003)	0.4
RECORD 1 ^[62] (N = 4541)	Rivaroxaban 10 mg daily (31-39 d)	40 mg daily (31-39 d)	1.1% (18/1595)	3.7% (58/1558)	n/a (< 0.001)	0.3% (6/2209)	0.1% (2/2224)	0.18
RECORD 2 ^[63] (N = 2509)	Rivaroxaban 10 mg daily (31-39 d)	40 mg daily (10-14 d)	2.0% (17/864)	9.3% (81/869)	n/a (< 0.0001)	0.08% (1/1228)	0.08% (1/1229)	n/a
ADVANCE 3 ^[73] (N = 5407)	Apixaban 2.5 mg BID (32-38 d)	40 mg daily (32-38 d)	1.4% (27/1949)	3.9% (74/1917)	< 0.001 (< 0.001)	0.8% (22/2673)	0.7% (18/2659)	0.54
STARS J-5 ^[75] (N = 610)	Edoxaban 30 mg daily (11-14 d)	20 mg BID (11-14 d)	2.4% (6/255) ¹	6.9% (17/248) ¹	< 0.001 (0.016)	2.6% (8/303) ²	3.7% (11/301) ²	0.48

¹All events were asymptomatic DVT. ²Rate of major and clinically relevant non-major bleeding. TSOA: Target specific oral anticoagulant; RE-NOVATE: The extended thromboembolism prevention after hip surgery; RECORD: Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE; STARS: Studying thrombosis after replacement surgery.

served in patients receiving both dabigatran and neuraxial anesthesia during three of four phase III studies (excluded RE-NOVATE II)^[57]. As previously noted, the risk of bleeding in Phase III studies of dabigatran in orthopedic surgery patients was not increased by concurrent NSAID or antiplatelet drug use^[50].

Rivaroxaban in THA

Rivaroxaban was initially evaluated in the THA population in three phase II studies. A dose-ranging study^[58] determined an acceptable safety profile for rivaroxaban when orally dosed between 2.5 to 30 mg twice daily or 30 mg once daily after THA. A phase II b study^[59] evaluated rivaroxaban 2.5 to 30 mg twice daily versus enoxaparin 40 mg subcutaneously once daily after THA and found that only rivaroxaban 2.5 to 10 mg twice daily compared favorably to enoxaparin. A second phase II b study^[60] evaluated rivaroxaban 5 to 40 mg once daily versus enoxaparin 40 mg daily. No dose-dependent response was seen with rivaroxaban and the rate of VTE; however, the incidence of bleeding did correlate with rivaroxaban in a dose-dependent manner. Based on these results, investigators recommended that rivaroxaban given as 10 mg once daily be evaluated in phase III studies. The recommendation was corroborated by a pharmacokinetic and pharmacodynamics analysis conducted by Mueck *et al*^[61] in THA patients.

The four Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE (RECORD) studies provided the basis for rivaroxaban's approval for VTE prophylaxis following orthopedic surgery. RECORD 1^[62] (n = 4541) and RECORD 2^[63] (n = 2509) evaluated the efficacy and safety of rivaroxaban following THA (Table 3). Both studies were randomized and double-blinded in comparing oral rivaroxaban 10 mg once daily started 6-8 h after surgery to enoxaparin 40 mg subcutaneously

started the evening prior to surgery then continued once daily following surgery. The study protocol for RECORD 1 provided for continuation of each treatment for 31-39 d while in the RECORD 2 study, rivaroxaban was given for 31-39 d compared to a shorter course of enoxaparin given for 10-14 d. Both studies used a primary efficacy outcome measure of total VTE, including asymptomatic VTE detected with venography, plus all-cause mortality, and a primary safety outcome measure of major bleeding. A secondary efficacy outcome of major VTE including proximal DVT, non-fatal PE, and VTE-related death also was pre-defined in both studies^[62,63].

In RECORD 1 that compared rivaroxaban and enoxaparin for the same extended duration of treatment, total VTE or death occurred in 1.1% (18/1595) and 3.7% (58/1558) of patients receiving rivaroxaban and enoxaparin, respectively ($P < 0.001$). Furthermore, major VTE was observed in 0.2% (4/1686) and 2% (33/1678) in the rivaroxaban versus enoxaparin groups ($P < 0.001$). Rivaroxaban efficacy was determined to be superior to enoxaparin in both the intention-to-treat and per protocol analyses with similar rates of major and minor bleeding^[62].

Comparing extended duration rivaroxaban versus short-term enoxaparin, RECORD 2 observed a rate in any VTE or death of 2% (17/864) and 9.3% (81/869) with rivaroxaban and enoxaparin, respectively ($P < 0.0001$). Major VTE was observed in 0.6% (6/961) patients receiving rivaroxaban and 5.1% receiving enoxaparin ($P < 0.0001$). Rivaroxaban superiority was again determined. Moreover, the results of the RECORD-2 study added further evidence supporting the use of extended thromboprophylaxis beyond 10-14 d after THA^[63].

An additional prospective non-interventional study has been conducted to validate the findings of the RECORD program. The Xarelto[®] in the Prophylaxis of

Post-surgical VTE after Elective Major Orthopedic Surgery of Hip or Knee (XAMOS) investigation by Turpie *et al.*^[64] included 17413 patients undergoing orthopedic surgery including both THA and TKA who received either rivaroxaban 10 mg once daily or conventional thromboprophylaxis, the majority of which included LMWH (81.7%). A focused comparison was made between those receiving rivaroxaban and those receiving LMWH. The investigators determined a rate of symptomatic VTE in 0.9% of patients receiving rivaroxaban and 1.5% of patients receiving LMWH. This correlated with a statistically significant hazard ratio of 0.57 (95%CI: 0.41-0.81).

Major and minor bleeding rates were similar between rivaroxaban and enoxaparin in each of the RECORD studies as well as the non-interventional XAMOS study^[62-64]. Wound complications including excessive wound hematoma, surgical site bleeding, and post-surgical wound infection were similar between rivaroxaban and enoxaparin in a pooled analysis of RECORD 1 and 2^[65]. However, the potential for an increased risk of wound complications associated with rivaroxaban has been brought into question by several recent institutional studies^[66-70]. In a multicenter analysis of 13123 major orthopedic surgery patients (including 5974 THA), Jameson *et al.*^[69] found an increased rate of wound complications including hematoma, superficial wound infection, and deep infection requiring return to surgery, with rivaroxaban compared to enoxaparin use (3.85% *vs* 2.81%, $P = 0.005$). Additionally, no incidence of spinal hematoma was observed with the use of rivaroxaban and neuraxial anesthesia in the RECORD program ($n = 4086$)^[71].

Apixaban in THA

Apixaban was not studied for use after THA in the phase II format; however, the results of the phase II study Apixaban prophylaxis in patients undergoing total knee replacement surgery (APROPROS)^[72] concluded that apixaban 2.5 mg twice daily had a similar efficacy and safety profile compared to enoxaparin for this indication and should be investigated in phase III clinical studies for use after orthopedic surgery. The Apixaban dosed orally *vs* Anticoagulation with injectable enoxaparin to prevent VTE (ADVANCE-3) study^[73] was a phase III double-blinded study that randomly assigned 5407 patients to either oral apixaban 2.5 mg twice daily or subcutaneous enoxaparin 40 mg once daily following an elective THA or a revision of a previously inserted hip prosthesis (Table 3). For those randomized to apixaban, therapy was initiated 12-24 h following the closure of the surgical site, where as enoxaparin therapy was initiated 12 h prior to surgery. Similar to other TSOA studies, the primary efficacy outcome included the occurrence of any VTE or death by any cause, and the primary safety outcome was a bleeding event categorized into major, clinically relevant non-major, and minor bleeding. A secondary efficacy outcome measured the occurrence of major VTE.

ADVANCE-3 demonstrated apixaban therapy to be more effective compared to enoxaparin in preventing

DVT, nonfatal PE, or death from any cause in patients after an average treatment duration of 34 d. Superiority analysis was conducted regarding apixaban *vs* enoxaparin after non-inferiority was established. Among the patients that were evaluated ($n = 3866$), the composite primary endpoint of adjudicated asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the treatment period occurred in 1.4% (27/1949) apixaban compared to 3.9% (74/1917) enoxaparin patients, respectively. Results demonstrated that apixaban was non-inferior ($P < 0.0001$) as well as superior ($P < 0.001$) to enoxaparin. Apixaban also was found to be superior to enoxaparin in preventing major VTE defined as proximal DVT, non-fatal PE, or VTE-related death (0.5% *vs* 1.1% $P = 0.01$). There was no significant difference in major and nonmajor clinically relevant bleeding between apixaban and enoxaparin groups^[73].

Edoxaban in THA

Edoxaban like apixaban, has been modestly studied for VTE thromboprophylaxis in THA patients. Two phase II and one phase III THA studies provided data that were combined with additional data in TKA patients to substantiate the drug approval in Japan. Each of the studies evaluated the same primary efficacy endpoint of total VTE during the treatment period, composed of asymptomatic DVT determined by venography at the end of the treatment period and any symptomatic VTE determined by objective means. The primary safety endpoint was major or clinically relevant but non-major bleeding events^[23].

Raskob *et al.*^[74] conducted a multicenter phase II dose-ranging study of 903 THA patients. Patients were randomized to receive oral edoxaban in dosages of either 15, 30, 60, or 90 mg given once daily or dalteparin 2500 IU subcutaneously initially, followed by 5000 IU once daily. Either drug therapy was started within 6-8 h postoperatively and continued for only 7-10 d. Edoxaban was associated with a significant ($P < 0.001$) dose-response effect, with VTE occurring in 28.2%, 21.2%, 21.2%, and 15.2% for the 15, 30, 60, and 90 mg daily doses, respectively. Each dose of edoxaban was associated with a significantly ($P < 0.005$) lower incidence of VTE, compared to dalteparin (43.8%). The incidence of bleeding was similar for all groups.

A smaller phase II b trial entitled studying thrombosis after replacement surgery (STARS) J-2^[75] was a similar study in 264 THA patients but compared only oral edoxaban 15 or 30 mg once daily to enoxaparin 20 mg subcutaneously twice daily (standard orthopedic prophylaxis dosage in Japan) for 11-14 d. The first dose of edoxaban was given within 6-8 h while enoxaparin was started 24-36 h postoperatively. Interestingly, all VTE events in this study were asymptomatic distal DVT. Results of the study demonstrated low VTE incidences in all groups that were not significantly different ($P > 0.05$), occurring in 3.8%, 2.8%, and 4.1% in the edoxaban 15mg, edoxaban 30 mg, and enoxaparin groups, respectively. Bleeding

events also did not differ between groups, with only one major bleeding event (edoxaban 30 mg group) occurring in the study^[23,75].

The STARS J-5 trial^[76] was a phase III study of oral edoxaban 30 mg once daily compared to enoxaparin 20mg subcutaneously twice daily for 11-14 d (Table 3). Results of the study in 610 THA patients demonstrated a significantly lower incidence of VTE of 2.4% in the edoxaban compared to 6.9% in the enoxaparin groups ($P < 0.001$ for noninferiority and $P = 0.0157$ for superiority). However, like STARS J-2, all VTE detected in the study were asymptomatic and primarily distal DVT, possibly due to a relatively small sample size. No difference was observed between the groups for major and clinically significant bleeding, occurring in 2.4% of edoxaban and 3.7% of enoxaparin patients, respectively ($P = 0.475$)^[23,76].

Comparison of TSOAs in THA

It is important to note that there have been no direct comparisons between TSOAs for thromboprophylaxis in THA. However, several investigators have published systematic analyses that attempt to give perspective regarding the comparable efficacy and/or bleeding risk of individual new agents^[77-80]. At least two meta-analyses have provided results that indirectly compared the efficacy and safety of the TSOAs, while one other meta-analysis focused solely on the safety^[77-81].

Dabigatran, rivaroxaban, and apixaban were indirectly compared by Gómez-Outes *et al.*^[78] based on study results that compared the given TSOA to enoxaparin. Eight of 16 included studies were in THA patients but results of the indirect comparisons were not separated by orthopedic surgery type. In this analysis, rivaroxaban tended to be associated with a lower relative risk (RR) for symptomatic VTE but also a greater RR for clinically relevant and major bleeding, although no differences were statistically significant. A random effects meta-analysis performed by Loke *et al.*^[79] included nine studies three of which were conducted in elective THA patients. They found that in THA patients, rivaroxaban 10mg daily compared to dabigatran 150 or 220 mg daily was more effective in preventing VTE (RR 0.46) but caused more bleeding (RR = 1.14)^[79]. In a similar indirect comparison, Alves *et al.*^[80] reported no differences between rivaroxaban and apixaban for total or major bleeding safety in the subgroup of patients undergoing THA.

A recent meta-synthesis by Adam *et al.*^[81] analyzed six previous systematic reviews that compared the TSOAs to other thromboprophylaxis agents, primarily LMWHs. As would be expected, their findings mirror previous conclusions regarding the individual TSOAs. However, they also noted that the strength of evidence was greater for FXa inhibitors than for dabigatran comparisons to LMWH.

PHARMACOECONOMIC CONSIDERATIONS OF TSOA USE IN THA

The economic burden associated with VTE has been well

established and the use of thromboprophylaxis has lessened this burden following major orthopedic surgery^[82-84]. LMWH was determined to be a cost-effective alternative to warfarin largely due to a significant comparative reduction in VTE with LMWH and the avoidance of monitoring costs associated with warfarin^[85]. With the approval of TSOAs, newer pharmacoeconomic analyses comparing TSOAs to LMWH have been performed to assess their potential economic impact.

Despite a similar incidence of VTE and bleeding in the RE-NOVATE study, Wolowacz *et al.*^[86] determined that dabigatran was less costly than enoxaparin, largely due to comparative medication costs associated with each agent in the British Health Service, providing a potential advantage for dabigatran use over LMWH after THA. McCullagh *et al.*^[87] sought to determine the cost-effectiveness of both dabigatran and rivaroxaban compared to enoxaparin in the Irish Healthcare System. The results of the RE-NOVATE and RECORD 2 studies were used to estimate the expected efficacy and safety outcomes after THA associated with the use of each TSOA, respectively. A base-case analysis showed that the 35 d use of rivaroxaban was more cost-effective than either 35 d of dabigatran or 10-14 d of enoxaparin. The results were not significantly affected by sensitivity analyses.

In a pharmacoeconomic model utilizing the pooled results from the RECORD 1 and RECORD 2 studies, Duran *et al.*^[88] determined that rivaroxaban significantly reduced the cost associated with THA by 511.93 US dollars per patient compared to enoxaparin. The finding was attributed to a 0.0145 reduction in symptomatic VTE per patient over a one year time period. The cost effectiveness of rivaroxaban was maintained throughout the sensitivity analysis that included different potential drug costs, the range of event rates observed in clinical studies, along with other variables that could impact healthcare cost following a THA. Supporting these results, Kwong *et al.*^[89] has more recently observed a similar cost savings with rivaroxaban compared to enoxaparin when also including the all-cause mortality results provided in the RECORD studies as part of the economic analysis.

Mahmoudi *et al.*^[90] pooled results of phase II and III orthopedic studies evaluating both rivaroxaban and apixaban to assess the impact of the FXa inhibitors as a class. Including multiple doses of each FXa inhibitor and assuming a 10-14 d duration of thromboprophylaxis, the investigators found a 135 US dollar reduction per patient associated with FXa inhibitor compared to LMWH (enoxaparin or dalteparin) use following THA in the 180 d post-surgery period. The cost effectiveness associated with the FXa class was maintained throughout all sensitivity analysis of cost variables.

The potential cost savings associated with the TSOAs, particularly rivaroxaban, are based on reductions in the expected incidence of symptomatic VTE events, as well as a reduction in administration and monitoring costs, while taking into account the potential for, and cost of major bleeding complications.

ANTICOAGULATION MONITORING AND REVERSAL OF TSOAS

The most challenging aspect regarding use of one of the TSOAs centers on the issue of reversing the anticoagulant effect. Limited clinical data especially in humans are available to address the issue of reversal and two factors complicate the matter. First, there are no well accepted and widely available laboratory methods for monitoring the new agents, meaning the routine assessment of anticoagulation intensity during reversal is impaired. Second, there are no direct acting antidotes for either dabigatran or any of the FXa inhibitors. Nevertheless, recommendations have been made in treatment guidelines regarding how to manage anticoagulation reversal of the new agents, and several recent reviews on the topic have been published^[91-93]. Moreover, some groups have offered consensus expert opinions by the authors regarding optimal approaches for anticoagulation reversal of the new agents^[93,94].

As previously noted, the risk of bleeding with the new agents is similar to that seen with other anticoagulants. Minor or major bleeding may be encountered in patients or reversal may be needed for an urgent invasive procedure. As such, the approach to management of anticoagulant reversal must be individualized as is the case with older established anticoagulants. Patient assessment for bleeding risk also is similar and increased risk is associated with anticoagulation intensity, a history of bleeding, advanced age, comorbid conditions, and other drug therapy such as concomitant antiplatelet drugs^[91]. Attention, particularly for dabigatran, should be given to renal status which correlates with the half-life and therefore the anticoagulation intensity for the new agents^[16,18,21]. Factors associated with increased bleeding risk are more common in the elderly population who represent a majority of THA patients.

Anticoagulation monitoring of TSOAs

Because of the more predictable anticoagulant response of the TSOAs, routine laboratory monitoring was not performed in major clinical studies of the new oral anticoagulants. However, identification of a laboratory monitoring test to assess the anticoagulant intensity of a given agent could greatly assist during reversal. Moreover, laboratory testing could have value to determine if bleeding risk is correlated with certain patient factors such as renal impairment or age and thereby identify patients at greater risk, to detect nonadherence or overdose, and to assess the impact of drug interactions^[95]. Several laboratory assays have been evaluated as monitoring tests to assist in reversal decisions with the TSOAs.

The common anticoagulation tests prothrombin time (PT) and activated partial thromboplastin time (aPTT) are readily available but react differently to the TSOAs. The PT test is of limited utility since its value varies according to the thromboplastin reagent used, and conversion to the International Normalized Ratio (INR) further in-

creases variability. If a reagent sensitive to rivaroxaban is used, the PT can be used to detect and roughly quantify an anticoagulant effect from that agent; it is unreliable to detect dabigatran or apixaban. In contrast, the aPTT test has been used to monitor dabigatran and a normal test value suggests a minimal or absent anticoagulant effect from the drug^[96,97]. The aPTT test result elevation was correlated with the dosage and serum concentrations of dabigatran in THA patients in the BISTRO I trial, but the correlation was nonlinear^[91,52]. The aPTT test result is also prolonged with the FXa inhibitors but effects are weaker than those on the PT test^[91].

Samama *et al.*^[98] recently determined the effects of dabigatran and rivaroxaban on the various coagulation tests in 106 patients receiving the drugs for major orthopedic surgery, including 36 who underwent THA. As would be expected, they found that the aPTT was sensitive to dabigatran and the PT was sensitive to rivaroxaban. Perhaps more importantly however, results also showed significant inter-individual variability in the peak serum concentration for each drug, indicating considerable variation in drug response and suggesting the value of laboratory monitoring.

Since the TSOAs “target” individual coagulation factors for their anticoagulant effect, laboratory tests more specific to those targets should have utility. The thrombin time (TT) test is affected by dabigatran but is very sensitive to the drug effects, rendering it a qualitative measure at typical drug concentrations. However, it can be used to exclude a dabigatran drug effect^[92,95,96]. Liew *et al.*^[96] suggested a normal aPTT result combined with a prolonged TT indicated low anticoagulation intensity with dabigatran, whereas prolonged results for both tests would indicate full anticoagulation. The Hemoclot test is a dilute TT already used for direct thrombin inhibitors hirudin and argatroban. The test has been shown to best correlate with dabigatran serum concentrations in a linear manner^[99]. Presently, the Hemoclot test is available in Canada and Europe, with approval pending in the United States^[96]. Finally, the ecarin clotting time (ECT) is sensitive to dabigatran serum concentrations across the usual therapeutic range but the test is costly, not widely available, and used primarily in research settings^[93,96].

Anti-factor Xa assays are widely available in practice settings for monitoring the effects of LMWH, and are logical for use to monitor rivaroxaban, apixaban, and edoxaban. However, the assay must be modified with calibrators specific to the given FXa inhibitor. Calibrators for the new drugs are becoming available and the test will likely emerge as the preferred measure of anticoagulation intensity associated with the FXa inhibitors^[92,93,95,96].

Anticoagulation reversal of TSOAs

Reversal of the anticoagulant effect of a TSOA follows the same principles utilized for older anticoagulant agents, particularly warfarin. If reversal is nonemergent or occurring in the patient suffering only mild bleeding, withholding the anticoagulant, monitoring hematologic

and coagulation tests as discussed above, and providing supportive care such as maintaining good urinary output will suffice. If the TSOA was taken within the past 2 h (or overdose is suspected), activated charcoal can be considered to reduce drug absorption. Because the drug half-lives of the new agents are shorter at approximately 8-16 h even in the elderly, the drug serum concentration will significantly decline in a 24 h period. One caveat that must be remembered is the effect of renal insufficiency to slow elimination, particularly with dabigatran^[91]. Several investigators have offered suggestions for timing of the discontinuation of the new oral anticoagulants before an elective or nonemergent surgery^[92,93,100].

Anticoagulation reversal of a TSOA in the patient with moderate to severe bleeding or in need of urgent surgery is more challenging. No specific antidote exists for any of the new oral agents, although work is ongoing by van Ryn *et al.*^[101] to evaluate a promising humanized antibody fragment against dabigatran. Lu *et al.*^[102] has developed a modified and inactive form of factor Xa that may function as a universal antidote to all factor Xa inhibitors.

For removal of a TSOA from the body, the pharmacokinetic differences between dabigatran and the factor Xa inhibitors have relevance and affect recommended modalities. Since dabigatran has low protein binding, hemodialysis can effectively remove the drug. Stangier *et al.*^[66] determined that over 60% of a single 50 mg dose of dabigatran was removed by hemodialysis after 2 h in a small study of patients with end-stage renal failure. The combination of high-dose recombinant factor VIIa and hemodialysis has been used to successfully treat a massive postoperative bleed in a patient who underwent cardiac surgery^[103]. Charcoal hemoperfusion may also represent an effective way to remove dabigatran^[94]. Both of the modalities appear as recommendations for dabigatran removal by consensus groups^[93,94,104]. However, while these methods are effective to remove dabigatran and presumably reverse its anticoagulant effect, both have limited application since availability is low, vascular access is required, and the time to implement is often prolonged^[92,94,96]. In contrast, high protein binding characterizes rivaroxaban (92%-95%) and apixaban (84%-87%), meaning a significant amount of either drug is unlikely to be removed by hemodialysis or hemoperfusion^[93,94].

Since no specific antidote exists and methods to remove drug from the system are limited, reversal of a TSOA's anticoagulant effect has been focused on the use of hemostatic agents and coagulation factor replacement. Traditional approaches used with warfarin have no or very little benefit in patients who are anticoagulated with the new agents. Specifically, vitamin K has no effect to reverse anticoagulation and fresh frozen plasma (FFP) requires long preparation time and large volumes, and has not been shown to have value for bleeding due to a TSOA^[94,96]. The use of FFP has given way to use of prothrombin complex concentrates (PCC) even for warfarin reversal^[105].

Recently, interest in the use of hemostatic agents

for reversal of anticoagulation with the TSOAs has focused on use of PCC products that contain concentrated amounts of vitamin K dependent clotting factors and are available in several forms. PCCs include products that contain three (factors II, IX, and X) or four (II, VII, IX, and X) virally inactivated clotting factors, and an activated product (also known as factor eight inhibitor bypassing activity or FEIBA) that contains an activated factor VII with inactivated factors II, IX, and X. Factor VII alone is also available as a recombinant product that is in activated form and can be added to the three-factor PCC to essentially make the four-factor PCC that has only recently become available in the United States^[92,93].

Despite the extensive interest in the use of PCCs to reverse anticoagulant effects of the TSOAs, there is a paucity of data especially in humans. The majority of data regarding the use of PCCs comes from preclinical animal and phase I *in vitro* and *ex vivo* studies^[92,93]. An extensive review of those data is beyond the scope of this article; an excellent review was recently published by Dickneite *et al.*^[106].

In their recent review, Thigpen and Limdi^[92] described 5 case reports of severe bleeding due to dabigatran that were treated with factor replacement, including only 2 patients who received a PCC product. Eerenberg *et al.*^[107] conducted a randomized, double-blind, crossover study of a four-factor PCC (Cofact[®]) effect on dabigatran and rivaroxaban's effect on coagulation assays in 12 healthy men. The PCC reversed coagulation changes induced by rivaroxaban but had no effect on coagulation changes associated with dabigatran. In contrast, a recent retrospective, observational study of five emergency room patients who received a four-factor PCC (Octaplex[®]) for urgent reversal of dabigatran-associated bleeding showed that PCC product administration was associated with normalization of the aPTT ratio in the single patient with an elevated ratio at admission^[108]. Understandably, a recent clinical practice guideline states the hemostatic factor products "should be considered" for use in "ongoing, life-threatening bleeding," a statement that reflects the lack of human clinical data addressing this issue^[109]. Nevertheless, Alikhan *et al.*^[110] has recently published algorithms for the management of dabigatran in the settings of bleeding, a need for emergency surgery, and overdose that give recommendations for the use of factor replacements. Nutescu *et al.*^[93] have similarly given recommendations for anticoagulation reversal of dabigatran, rivaroxaban, and apixaban based on the level of urgency.

Finally, several aspects likely affect interpretation of available data surrounding the use of factor replacements. Animal-derived data while useful may not accurately reflect the coagulation process in humans. Some three-factor PCCs may have a short duration of benefit if factor VII is a key factor to sustain reversal action. While activated PCCs such as FEIBA present a known increased risk for thrombosis, they may be required to reverse anticoagulation for some or all of the TSOAs. Variation in the reversal of anticoagulation by various

PCCs may be related to the product composition, some which contain antithrombotic proteins C and S; it is unknown which factor(s) in a PCC product is/are critical to achieve reversal. And finally, it must be remembered that a correlation of what appears to be favorable effects on various laboratory tests with a decreased bleeding risk or intensity has not been established in humans^[92-94,106].

CONCLUSION

TSOAs offer several clear advantages to traditional anti-thrombotic agents including rapid onset of action, short half-life, predictable pharmacokinetics and pharmacodynamics, and minimal drug-drug interactions. Dabigatran, rivaroxaban, and apixaban have been approved for thromboprophylaxis after THA in many countries, while rivaroxaban and apixaban are currently the only agents approved by the FDA in the United States, and a fourth additional agent, edoxaban, has been approved only in Japan for this indication. TSOAs have provided safe and effective options for thromboprophylaxis after THA and represent a cost-effective alternative to the most widely used LMWH class of anticoagulants. Although long-term clinical experience is lacking, and the ability to reliably monitor or reverse the anticoagulant effect of the agents is still under development, TSOAs have established a new approach to thromboprophylaxis after THA.

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