New oral anticoagulants in venous thromboembolism prophylaxis in orthopaedic patients: Are they really better?

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Summary

Prophylaxis against venous thromboembolism (VTE) is considered standard of care. Appropriate chemoprophylaxis for VTE has been mandated by the United States government agencies and consumer groups. However, controversies exist regarding the most clinically relevant and safe chemoprophylaxis protocols in patients undergoing joint replacement surgery. Thus, this paper reviews the clinical efficacy and safety of newer oral anticoagulants. A literature search was performed for oral anticoagulants in advanced stages of development using PubMed and abstracts from thrombosis meetings. Most clinical trial data have demonstrated equal or superior efficacy in venographic endpoints in comparison to low-molecular-weight heparins (LMWH). However, bleeding complications have been reported to occur with oral anticoagulants as frequently as or more frequently than with LMWH. Other potential complications reported include liver enzyme elevation and cardiac irregularities. It remains to be established whether newer oral anticoagulants will be better alternatives to the current standard-of-care in real-life medical clinical practice.

Keywords

Oral anticoagulants, prophylaxis, safety, venous thromboembolism

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Introduction

Patients undergoing major orthopaedic surgery are at particularly high risk of venous thromboembolism (VTE) (1). Without effective thromboprophylaxis the incidence of objectively confirmed, hospital-acquired, deep-vein thrombosis is approximately 40% to 60% following total hip replacement (THR), total knee replacement (TKR), or hip fracture surgery (1). Therefore, prophylaxis against VTE is considered standard of care. Furthermore, risk stratification and administration of appropriate pharmacologic prophylaxis for VTE has been mandated by a variety of US government agencies and consumer groups (1–3).

However, controversies exist with regard to the most clinically relevant and the safest pharmacological prophylaxis in orthopaedic patients (4). The American College of Chest Physicians recommends that patients undergoing high-risk orthopaedic procedures receive prophylaxis with a low-molecular-weight heparin (LMWH), fondaparinux, or an adjusted-dose vitamin K antagonist for at least 10 days post-surgery and for up to 35 days after THR or hip fracture surgery (1). LMWHs are considered to be among the most clinically efficacious pharmacological prophylaxis and are used as the standard-of-care in many medical communities (1). One of the greatest concerns from orthopaedic surgeons with regard to using anticoagulants post major joint replacement surgery is bleeding at the surgical site (5). Warfarin is the other agent frequently used in the United States. It offers the advantage of oral administration. However, warfarin is limited by delayed onset of action, narrow therapeutic range, drug-drug and drug-food interactions, and monitoring required for dose adjustment (6, 7).

New oral anticoagulants are being developed to improve the efficacy and safety of pharmacological VTE prophylaxis. Currently, several oral anticoagulants are in advanced stages of clinical development and regulatory approval process. Most clinical trial data have demonstrated equal or superior efficacy in comparison to LMWHs based on venographic endpoints. Bleeding complications, however, have been reported to occur as frequently, or more frequently than, with LMWH. Other potential complications, such as liver enzyme elevation and cardiac irregularities, have also been reported with these newer agents. Thus, it remains to be established if newer oral anticoagulants will be better alternatives to the current standard-of-care in clinical practice.

The purpose of this paper is to critically review the available clinical data with regard to the safety profiles of these newer oral anticoagulants. Specific areas of focus include: liver toxicity, cardiac complications, drug-drug interactions, bleeding events, and renal impairment.

Methods

MEDLINE, EMBASE, and SCOPUS databases were searched from inception through to October 2010 to identify relevant English-language clinical trials, abstracts, and articles related to the new oral anticoagulants dabigatran etexilate, rivaroxaban, and apixaban in orthopaedic surgery. In addition, the reference lists of identified articles were searched for further relevant publications. In the absence of peer-reviewed publications, some information was extracted from the product monographs. Pertinent review articles on VTE prophylaxis were also included.

History of earlier oral anticoagulants

Ximelagatran

The direct thrombin inhibitor ximelagatran, a pro-drug of melagatran, was the first in the new class of oral anticoagulants. Ximelagatran was initially approved by European regulatory agencies based on clinical trial data in orthopaedic joint replacement patients (7, 8). The trial's design included a regimen of preoperatively-initiated subcutaneous injection of melagatran followed by oral ximelagatran for up to 11 days (9, 10). No signs of liver toxicity were observed with short-term prophylaxis. However, in a study of extended treatment (35 days), ximelagatran was associated with an increased risk of liver toxicity (8, 11). In 2% of patients treated with ximelagatran an increase in alanine aminotransferase (ALT) occurred after treatment withdrawal (8). In comparison, no patients treated with enoxaparin showed elevated ALT after treatment cessation (8). The liver toxicity seen with ximelagatran was unpredictable. It did not appear to be dose related and was considered to be the principal cause of death in three patients (7). As a result, the clinical development of ximelagatran was terminated and later withdrawn from the market (12).

Razaxaban

Razaxaban was the first new oral factor Xa inhibitor to be developed (13). In phase I clinical trials involving young and elderly healthy subjects razaxaban was well tolerated with only minor bleeding deemed clinically insignificant (13). A phase II clinical trial in patients undergoing TKR demonstrated higher bleeding rates with razaxaban twice daily (razaxaban 25 mg 0.7%; 50 mg 4.1%; 75 mg 3.5%; and 100 mg 5.8%) compared with enoxaparin 30-mg twice daily (0.0%) (14). Due to the increased bleeding with razaxaban the three highest doses were stopped prematurely and razaxaban was later discontinued from further clinical development in 2005.

With these as a reference, clinical trial data of any new oral anticoagulants need to demonstrate an efficacy profile that is at least non-inferior to LMWHs or warfarin. Moreover, their safety profile should be equal or superior to existing pharmacological prophylaxis agents.

Property	Ximelagatran	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Thrombin	Thrombin	Factor Xa	Factor Xa
Pro-drug	Yes	Yes	No	No
Bioavailability (%)	~20	~6.5	80–100	50–85
Time to peak drug level (hours)	2–3	0.5–2	2–4	3
Half-life (hours)	4–5	11 in healthy young subjects 14–17 in patients	5–9 in healthy subjects 7–11 in patients	9–14
Frequency of administration	Twice daily	Once daily or twice daily	Once daily	Twice daily
Renal excretion (%)	>80	85	66	25
Specific antidote	No	No	No	No
Regulatory status	Withdrawn from world market in 2006	Approved in all EU member states and Canada for VTE prophylaxis after TKR and THR	Approved in Canada and all EU member states for VTE prophylaxis after TKR and THR. Under US FDA review	None

EU, European Union; VTE, venous thromboembolism; TKR, total knee replacement; THR, total hip replacement; FDA, Food and Drug Administration.

Table 1: Properties of oral anticoagulants ximelagatran, dabigatran etexilate, rivaroxaban, and apixaban (15–20).

New oral anticoagulants

Several new oral anticoagulants are currently under development. The three new oral anticoagulants with the most advanced clinical trial programs are dabigatran etexilate, rivaroxaban, and apixaban (▶Table 1) (15–20).

Dabigatran etexilate

Dabigatran etexilate is an oral pro-drug that is rapidly absorbed and converted to the direct thrombin inhibitor, dabigatran (21). Three phase III trials have been published comparing dabigatran to enoxaparin (▶Table 2) (22–24) and a fourth phase III trial was recently completed in THR. In addition, a meta-analysis of the three published phase III trials has been conducted (25, 26). Dabigatran was approved for VTE prophylaxis in patients undergoing THR and TKR in the European Union in April 2008 and in Canada in June 2008. Dabigatran was approved for use in stroke risk reduction in patients with non-valvular atrial fibrillation by the US Food and Drug Administration (FDA) in October 2010.

Rivaroxaban and apixaban

Rivaroxaban and apixaban are both direct inhibitors of factor Xa. These agents inhibit circulating factor Xa and also factor Xa bound within the prothrombinase complex (19, 27, 28). Four phase III trials have been completed comparing rivaroxaban to enoxaparin (▶Table 2) (29–32). Rivaroxaban was approved for the prevention of VTE in patients undergoing THR and TKR in Canada in September 2008, in the European Union in October 2008, and is currently under review by the FDA (33).

Three phase III trials have been published comparing apixaban to enoxaparin (▶Table 2) (28, 34–36) but it has not been approved for clinical use in any community.

Potential problems with the new oral anticoagulants

Several potential complications have been documented with these new oral anticoagulants.

Liver toxicity

Idiosyncratic drug reactions have been found to be the presumptive cause of more than one in ten of all cases of acute liver failure (37). Furthermore, drug-induced hepatic toxicity is the most common reason cited for the withdrawal of an approved drug on the market (38). The exact mechanisms responsible for the liver toxicity observed with ximelagatran have not been fully identified. It is, therefore, difficult to predict whether the newer oral direct thrombin or factor Xa inhibitors could cause similar toxicity (8). The severe liver toxicity induced with ximelagatran was only identified after the drug was approved in Europe (8). Elevations of ALT >3 x the upper limit of normal (ULN) occur at a frequency of approximately 5% of patients treated with unfractionated heparin or LMWHs (39, 40). However, these increases are generally transient, asymptomatic, and have not been associated with long-term adverse sequelae (39, 41, 42).

Clinical complication rates associated with liver toxicity have been assessed in a number of studies. In a phase I study the pharmacokinetics, pharmacodynamic, and safety profile of dabigatran were comparable in healthy subjects (n=12) and patients with

Table 2: Phase III trials of dabigatran etexilate, rivaroxaban, and apixaban in orthopaedic surgery patient populations (22–24, 29–32, 34–36).

Trial	RE-NOVATE[22]	RE-MODEL[23]	RE-MOBILIZE[24]	RECORD 1[29]	RECORD 2[30]	RECORD 3[31]	RECORD 4[32]	ADVANCE-1[34]	ADVANCE-2[35]	ADVANCE-3[36]
Population	THR	TKR	TKR	THR	THR	TKR	TKR	TKR	TKR	THR
Study drug	Dabigatran 150/220 mg od[a]	Dabigatran 150/220 mg od[a]	Dabigatran 150/220 mg od[b]	Rivaroxaban 10 mg od[e]	Rivaroxaban 10 mg od[e]	Rivaroxaban 10 mg od[e]	Rivaroxaban 10 mg od[e]	Apixaban 2.5 mg bid[d]	Apixaban 2.5 mg bid[d]	Apixaban 2.5 mg bid[d]
Active control	Enoxaparin 40 mg od[c]	Enoxaparin 40 mg od[c]	Enoxaparin 30 mg bid[d]	Enoxaparin 40 mg od[f]	Enoxaparin 40 mg od[f]	Enoxaparin 40 mg od[f]	Enoxaparin 30 mg bid[d]	Enoxaparin 30 mg bid[d]	Enoxaparin 40 mg od[f]	Enoxaparin 40 mg od[f]
Duration	28–35 days	6–10 days	12–15 days	31–39 days	31–39 days[g]	10–14 days	10–14 days	10–14 days	10–14 days	32–38 days
Study design	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority/ Superiority	Superiority	Non-inferiority/ Superiority	Non-inferiority/ Superiority	Non-inferiority	Non-inferiority	Non-inferiority/ Superiority

[a]First dose was half dose started 1–4 hours after surgery. [b]First dose was half dose started 6–12 hours after surgery. [c]Started the evening prior to surgery. [d]Started 12–24 hours after surgery. [e]Started 6–8 hours after surgery. [f]Started 12 hours prior to surgery. [g]Rivaroxaban for 31–39 days, enoxaparin for 10–14 days followed by placebo. THR, total hip replacement; TKR, total knee replacement; od, once daily; bid, twice daily.

moderate hepatic impairment (n=12) (43). Liver enzyme levels were monitored in a phase III trial of TKR patients (n=2,076) receiving 6–10 days of prophylaxis with once-daily dabigatran 150 mg or 220 mg compared with enoxaparin 40-mg once daily. Elevation of ALT levels >3 x ULN was reported in 3.7%, 2.8%, and 4.0% of patients, respectively, in the three groups. All of the abnormal values returned to baseline within four weeks (23). In another trial of prophylaxis with dabigatran for 28–35 days in patients after THR (n=3,494), elevation of ALT levels >3 x ULN were reported in 3% of patients receiving once daily 150 mg or 220 mg dabigatran and in 5% of patients receiving enoxaparin 40-mg once daily. All ALT levels returned to baseline or the ULN in the two-month follow-up period (22).

The phase II ODIXa-DVT trial compared treatment using a 12-week regimen of 10-, 20-, or 30-mg twice daily, or 40-mg once-daily rivaroxaban with enoxaparin 1-mg/kg twice daily for 5–7 days, followed by a vitamin K antagonist (adjusted-dose warfarin) for the remainder of the study period (44). Rivaroxaban was stopped prematurely in three patients because of elevated liver enzyme levels. One of these patients died 2.5 weeks later of carcinoma with liver metastases. One patient died of liver failure, likely due to hepatitis B infection. In the third patient, treatment was stopped after five days and the ALT and aspartate aminotransferase levels returned to below the ULN after treatment discontinuation without sequelae. There was no need to stop treatment in any of the patients in the enoxaparin group due to elevated liver enzymes and there were no liver-related deaths in this group. In a recent analysis of the RECORD clinical trial data by the FDA review panel, serious treatment-emergent liver enzyme elevation was seen in 0.27% of patients receiving rivaroxaban (n=6,183) compared with 0.18% in the enoxaparin group (n=6,200) (33).

No significant liver enzyme elevation was reported in earlier clinical trials of apixaban (28, 45). Liver enzyme monitoring was included in the ADVANCE-1 study comparing apixaban 2.5-mg twice daily to enoxaparin 30-mg twice daily in patients undergoing TKR. During the 60-day follow-up period, elevated aminotransferase and bilirubin levels were rare in both groups (0.1% vs. 0.2% and <0.1% vs. 0%, respectively) (34). The recent ADVANCE-2 study, which compared apixaban 2.5-mg twice daily to enoxaparin 40-mg once daily in patients undergoing TKR, illustrated similar total rates of elevated aminotransferase and bilirubin levels in both the apixaban and enoxaparin treated groups (2% vs.2% and <1% vs. <1%, respectively) (35). One patient, receiving apixaban, who died in the ADVANCE-2 trial had study treatment discontinued on day 6 of the study due to fever, jaundice and elevated aminotransferase and bilirubin levels. The adjudicated cause of death for this patient, on day 12 of the study, was "query infection and hepatitis leading to aspiration pneumonia and multi-organ failure". The authors note that a contribution of the study drug remains possible. The ADVANCE-3 trial compared apixaban and enoxaparin in THR with the same dosing regimen as ADVANCE-2, but with a longer duration of 32–38 days. Once again, similar total rates of elevated aminotransferase and bilirubin levels were reported (1.4% vs. 1.8% and 1.0% vs. 0.5%, respectively) (36). Additional data on liver enzyme elevation were available in the APPRAISE dose-ranging study of patients with acute coronary syndromes (n=1,715). Elevation of either ALT or aspartate aminotransferase >3 x ULN was reported in similar proportions of patients who received apixaban 2.5-mg twice daily (0.3%), 10-mg once daily (1.3%), 10-mg twice daily (0.9%), or 20-mg once daily (0.5%). These were actually lower than in the placebo group (3.4%) (46).

Cardiac toxicity

There are also concerns that these newer anticoagulants may cause a rebound effect after treatment cessation. This could manifest as an increase in arterial thromboembolic events (47). However, the ability to accurately assess the true potential impact of new oral anticoagulants on the rebound phenomenon may be limited in clinical trials. The pre-specified endpoints in clinical trials are commonly short term: at the end of the thromboprophylaxis period and generally less than three months after the study drug was stopped (47). Increased risk of arterial adverse events including myocardial infarction was reported in patients after terminating ximelagatran treatment (15). These findings raised concerns of a possible rebound effect. However, there were insufficient data to conclusively demonstrate such a correlation (47). A pro-arrhythmic effect is another potential clinical concern with these agents. A phase I study in 54 healthy subjects (mean age 62.4 years) specifically investigated the effect of rivaroxaban on QT-interval prolongation. Study data demonstrated that a single dose of rivaroxaban 15- or 45-mg did not prolong the QT interval (48). Further long-term studies are required to confirm these preliminary results.

▶Table 3 summarises some of the published data on acute coronary events in patients treated with the new oral anticoagulants and enoxaparin (15, 23, 24, 33, 47). These events were relatively low and similar in patients receiving dabigatran or enoxaparin (23, 24). In the RECORD studies the overall rate of cardiovascular events was similar between rivaroxaban (0.50%) and enoxaparin (0.63%) study groups (33). Adjudicated ischaemic stroke was reported in 0.19% of patients receiving rivaroxaban and 0.11% in the enoxaparin group. However, more ischaemic stroke events occurred after drug discontinuation in the rivaroxaban group (0.10%) than in the enoxaparin group (0.02%). In a phase II study of VTE prophylaxis following TKR 0.33% of patients in the apixaban group had a myocardial infarction and 0.55% had a stroke. No such events were reported in the enoxaparin patient group (28). In the ADVANCE-1 study the incidence of cardiovascular events was low in both apixaban and enoxaparin groups (0.1% vs. 0.3%, respectively) (34). Similar rates of myocardial infarction were reported in the recent ADVANCE-2 and ADVANCE-3 studies (<1% in both the apixaban and enoxaparin groups) (35, 36). In the ADVANCE-2 study, stroke occurred in two patients in the apixaban group (<1%) vs. none in enoxaparin group (0%) (35). Rates of stroke were similar in the ADVANCE-3 study, at <0.1%, in the apixaban group and 0.2% in the enoxaparin group (36). Further studies are required to more conclusively exclude any possible rebound effects after withdrawal of the new oral anticoagulants.

Drug and food interactions

Many patients undergoing joint replacement are elderly and/or have co-morbidities that require multiple medications, some of which may affect the pharmacokinetics of the anticoagulant. Warfarin is the most commonly used oral anticoagulant for VTE prophylaxis in joint replacement patients in the United States (5). However, warfarin has numerous well-characterised interactions with many commonly used drugs, several foods, and unregulated herbal supplements (▶Table 4) (6). These interactions are principally due to the hepatic elimination of warfarin which is mediated by the cytochrome P450 (CYP450) enzyme system (49).

There is a need for careful consideration of the mechanisms of drug metabolites of the new oral anticoagulants. Dabigatran is not metabolised by CYP450; however, it is a substrate for the efflux transporter P-glycoprotein which is known to have an impact on drug-drug interactions (50). Potent P-glycoprotein inducers or inhibitors could impact dabigatran metabolism and may be expected to affect its clinical efficacy and safety if used concomitantly (18, 51). Quinidine, a potent P-glycoprotein inducer, is commonly used to treat cardiac arrhythmias. Its use is contraindicated with dabigatran because it doubles the concentration of dabigatran and may thus increase the risk of bleeding (51). Dabigatran is also contraindicated with the concomitant use of other P-glycoprotein inhibitors such as verapamil or clarithromycin. Co-administration of dabigatran with amiodarone, another P-glycoprotein inhibitor, increases dabigatran AUC and C_{max} by approximately 60% and 50%, respectively (18). Dose reduction of dabigatran to 150-mg once daily is, therefore, recommended for patients on amiodarone treatment. In addition, potent P-glycoprotein inducers, such as rifampicin or the herbal remedy St John's Wort, may reduce the bioavailability of dabigatran (18). Caution is advised when considering co-administration of dabigatran with either of these agents.

There is a need for caution and close observation for signs of bleeding when dabigatran is used with non-steroidal anti-inflammatory drugs (18). Concomitant use of dabigatran and aspirin is not recommended (18). In clinical studies in patients with atrial fibrillation, high-dose dabigatran plus aspirin resulted in increased bleeding events (52, 53). In an open-label trial in patients with atrial fibrillation (n=502), the incidence of major bleeding was significantly more frequent in the group (n=64) treated with dabigatran 300-mg twice daily plus aspirin (4 events) than in the group (n=105) treated with dabigatran 300-mg twice daily without aspirin (0 events; $p<0.02$) (52). In the recent RE-LY study of dabigatran versus warfarin in patients with atrial fibrillation (n=18,113), approximately 20% of patients used aspirin (<100 mg per day) during the treatment period in each group, but no specific outcomes were reported (54).

CYP450 enzymes are involved in the metabolism of rivaroxaban and apixaban (16, 55). Rivaroxaban does not inhibit or induce any major CYP450 enzymes (16). However, approximately two-thirds of the administered dose of rivaroxaban is metabolised by the liver via CYP450-independent mechanisms (mainly CYP3A4/3A5 and CYP2J2) and a third is excreted unchanged by the kidneys (16, 56). Rivaroxaban is also a substrate for P-glycoprotein transporters. Therefore, the use of rivaroxaban is contraindicated in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir, as these drugs may increase rivaroxaban plasma concentrations. Such elevation may be clinically relevant and potentially result in an increased bleeding risk (16). Co-administration of rivaroxaban with other agents that inhibit only one of the elimination pathways, either P-glycoprotein or CYP3A4, may also potentially increase the rivaroxaban plasma concentration. Data from the RECORD trials showed that the rate of major or non-major clinically-relevant bleeding in patients receiving rivaroxaban plus a CYP3A4 or P-glycoprotein inhibitor was 3.5-fold higher than those receiving enoxaparin plus either a CYP3A4 or P-glycoprotein inhibitor (7% vs. 2%, respectively) (38). Co-administration of rivaroxaban with strong inducers of CYP3A4 (e.g. phenobarbitone, phenytoin, carbamazepine, St John's Wort) or with strong inducers of CYP3A4 and P-glycoprotein (e.g. rifampicin) is cautioned. The use of rivaroxaban with non-steroidal anti-inflammatory drugs is cautioned as some patients may have a greater pharmacodynamic response that could increase bleeding risk (16). In addition, data from the RECORD trials demonstrated higher bleeding in patients who received rivaroxaban with concomitant use of an opioid or a statin.

Table 3: Cardiovascular adverse event rates in venous thromboembolism prophylaxis clinical trials of total hip or knee replacement surgery.

Study	Regimens	Cardiovascular events, n/N (%)	
		On treatment	Off treatment
[a]FDA review[15, 47]	Ximelagatran 24 or 36-mg bid oral Warfarin adjusted to target INR 2.5	20/2,677 (0.75)* 5/1,907 (0.26)	NA
[b]RE-MODEL[23]	Dabigatran 150-mg od Dabigatran 220-mg od Enoxaparin 40-mg od	7/703 (1.00) 3/679 (0.44) 4/694 (0.58)	1/703 (0.14) 0 2/694 (0.29)
[c]RE-MOBILIZE[24]	Dabigatran 150-mg od Dabigatran 220-mg od Enoxaparin 30-mg bid	10/871 (1.15) 9/857 (1.05) 9/868 (1.04)	NA
RECORD1–4 analysis[33]	Rivaroxaban 10-mg od Enoxaparin 40-mg od or 30-mg bid	13/6,183 (0.21) 25/6,200 (0.40)	17/6,183 (0.28) 14/6,200 (0.23)
[d]ADVANCE-1[34]	Apixaban 2.5-mg bid Enoxaparin 30-mg bid	1/1,596 (<0.1) 4/1,588 (0.3)	1/1,596 (<0.1) 1/1,588 (<0.1)
[d]ADVANCE-2[35]	Apixaban 2.5-mg bid Enoxaparin 40-mg od	1/1,501 (<1) 1/1,508 (<1)	0 0
[d]ADVANCE-3[36]	Apixaban 2.5-mg bid Enoxaparin 40-mg od	5/2,673 (0.2) 4/2,659 (0.1)	4/2,599 (0.2) 1/2,576 (<0.1)

[a]Myocardial infarction/ischaemia/angina. [b]Adjudicated acute coronary events (confirmed unstable angina, myocardial infarction, and cardiac death). [c]Cardiac serious adverse events. [d]Myocardial infarction. *$p<0.05$ vs. warfarin. bid, twice daily; NA, not available; INR, international normalised ratio; od, once daily.

Table 4: Drug, food and dietary supplement interactions with warfarin (6).

	Anti-infectives	Cardio-vascular	Analgesics, anti-inflammatories, and immuno-logics	Central nervous system drugs	Gastrointestinal drugs and food	Herbal supplements	Other drugs
Potentiation							
Highly probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid Metronidazole Micronazole Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline	Cimetidine Omeprazole Fish oil Mango	Boldo-funugreek Quilinggao	Anabolic steroids Zileuton
Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Aspirin Celecoxib Dextropropoxphene Interferon Tramadol	Disulfiram Chloral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Grapefruit	Danshen Don quai Lycium barbarum L PC-SPES	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine
Inhibition							
Highly probable	Griseofulvin Nafcillin Ribavirin Rifampicin	Chlestryamine	Mesalamine	Barbiturates Carbamazepine	High vitamin K content foods/enteral feeds Avocado (large amounts)		Mercaptopurine
Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chloradiazeposide	Soy milk Sucralfate	Ginseng	Chelation therapy Influenza vaccine Multivitamin supplement Raloxifene HCL

The risk of major or clinically relevant bleeding was 2.52-fold (95% confidence interval [CI] 1.72–3.71) higher with concomitant use of opioids and 1.52-fold (95% CI 1.07–2.17) higher with the use of a statin (33). For patients receiving enoxaparin the relative increased bleeding risk was 1.31-fold (95% CI 0.87–1.96) and 1.26-fold (95% CI 0.81–1.95) for concomitant use of opioids and statins. This increase did not reach statistical significance (33).

The elimination of apixaban involves multiple pathways including intestinal and renal excretion (55). *In vitro* studies have demonstrated that apixaban did not have any effect on any of the CYP450 isoforms investigated. However, the primary metabolite of apixaban, the *O*-demethylated product, is formed mainly by CYP3A4 (55).

Small-scale studies in healthy volunteers have investigated the effect of food on the pharmacokinetics of dabigatran and rivaroxaban (57, 58). Following consumption of a high-fat, high-caloric breakfast by volunteers (n=18), the absorption of dabigatran 150 mg was delayed, but the extent of absorption was not different compared with the fasting state (57). In addition, a reduction in inter-individual variability for C_{max} and AUC was noted with the high-fat diet. In a similar study of rivaroxaban (20 mg) in 10 subjects, inter-individual variability for pharmacokinetic parameters was lower in the non-fasting state. The presence of food delayed the time to maximum concentration, increased C_{max}, AUC, and maximum prothrombin time prolongation compared with fasting patients (58). The type of food, either a high-fat, high-caloric breakfast (n=6) or a high-carbohydrate meal (n=4), did not differ. Currently, no data are available on food interactions with apixaban.

There is increasing awareness regarding the safest drug dosing and schedule of anticoagulants, particularly in the elderly. Currently there is limited experience with new oral anticoagulants in elderly patients. The manufacturer of dabigatran recommends reducing the dose to 150 mg in patients aged older than 75 years as well as close clinical surveillance due to potential increased bleeding risk (18).

Elderly patients receiving rivaroxaban have approximately 1.5-fold higher mean plasma AUC values than younger patients

Table 5: Dosing recommendations in patients with renal insufficiency (16–18, 62).

	Moderate (creatinine clearance 30–50 ml/min)	Severe (creatinine clearance <30 ml/min)
Enoxaparin	No dose adjustment recommended but careful observation of patients for signs or symptoms of bleeding	Indication-specific dose adjustments are recommended
Dabigatran	Treat with caution Recommended starting dose of 75 mg, and continued at 150-mg daily, taken as two capsules of 75 mg each	Contraindicated
Rivaroxaban	Use with caution in patients receiving concomitant treatment with inhibitors of CYP3A4 or P-glycoprotein Consider benefit-risk of therapy carefully for patients with a creatinine clearance close to 30 ml/min or with a potential for deterioration, and monitor renal function No dose adjustment specified	Contraindicated in Canada (19) Cautioned with creatinine clearance 15–29 ml/min, and contraindicated with creatinine clearance <15 ml/min in the European Union (20)
Apixaban	No data available	No data available

(16, 17). This was suggested to be mainly due to reduced renal clearance in the elderly. At present there is no recommendation of dose adjustment of rivaroxaban in the elderly. In contrast, there are extensive clinical data on the use of enoxaparin in the elderly over the past 20 years (59–61). In general, there is no need for dose adjustment in the elderly unless kidney function is impaired (62).

Postoperative nausea and vomiting

Initiation and maintenance of oral anticoagulants is not possible in patients with active vomiting, bowel obstruction, and colonic distension. However, post-operative nausea and vomiting is one of the most common complications following anaesthesia and surgery (63). In the RE-NOVATE trial comparing dabigatran (n=1,163) with enoxaparin (n=1,154) in patients undergoing THR, nausea was reported in 22% and 25% of patients, respectively (22). The rate of vomiting was also similar between the two groups (16% vs. 17%, respectively) (22). Furthermore, in a recent trial of patients with atrial fibrillation, dyspepsia was significantly more frequent in patients treated with dabigatran 110 mg or 150 mg (11.8% and 11.3%) than with warfarin (5.8%; $p<0.001$ for both comparisons) (54). In an analysis of aggregate data from RECORD trials comparing rivaroxaban (n=4,657) with enoxaparin (n=4,692), the rates of nausea were equal (10.8% for both) and the rates of vomiting were similar (9.6% vs. 10.2%, respectively) (64). In the recent ADVANCE-2 study, the rates of nausea and vomiting in patients receiving apixaban and enoxaparin were similar (7% vs. 8% and 5% vs. 6%, respectively) (35).

Renal impairment

Up to 85% of dabigatran and 66% of rivaroxaban is excreted through the renal system (43, 56). Therefore, the half-life of these drugs may be prolonged in elderly patients who may have an age-related reduction in drug clearance and in those patients with marginal renal clearance. This could potentially lead to complications. The current approved recommendations for the use of new oral anticoagulants and enoxaparin in patients with renal insufficiency are presented in ▶Table 5 (16–20, 62).

This important clinical issue is made more confusing with different recommendations in the approved labelling of rivaroxaban between Canada and Europe (16, 17). In Canada rivaroxaban is contraindicated in patients with creatinine clearance <30 ml/minute (min) (16), whereas in Europe it is contraindicated in patients with creatinine clearance <15 ml/min and only cautioned in patients with creatinine clearance of 15–29 ml/min (17). Apixaban is eliminated predominantly through the biliary/faecal route and, therefore, it is less likely to accumulate in patients with renal insufficiency (42, 56).

Clinical bleeding events with the new oral anticoagulants

Bleeding events are the most important clinical complication and the major safety concern with any anticoagulant agent (65, 66). In a recent survey of practices in VTE prevention, approximately half of all US orthopaedic surgeons stated that bleeding was of greater concern than VTE in their choice of VTE prophylaxis (67). LMWHs have been used worldwide for nearly 20 years. Their bleeding profile has been reported in numerous clinical trials and post-marketing studies. Following major orthopaedic surgery, the incidence of clinically relevant bleeding complications with LMWHs ranges from 0.9% to 9.3% (68–72). However, LMWHs can be partially reversed (60%) using protamine in extreme clinical settings if needed (73). In contrast, the new oral anticoagulants do not have specific reversal agents yet (66). Thus, it is particularly important to evaluate the risk of bleeding with the new oral anticoagulants.

Table 6: Bleeding rates in venous thromboembolism prophylaxis clinical trials of total hip or knee replacement surgery.

Study	Indication (N)	Regimens	Duration, days	Major/clinically significant bleeding[a]	Major bleeding	Major/surgical site bleeding	Clinically relevant non-major bleeding	Minor bleeding
Dabigatran etexilate								
BISTRO I[21]	THR (289)	Dab 12.5-, 25-, 50-, 100-, 150-, 200-, 300-mg bid; and 150-, 300-mg od	6–10	2.4% Dab 150-mg od[b]	0% Dab 150-mg od[b]	NA	2.4% Dab 150-mg od[b]	95.1% Dab 150-mg od[b]
BISTRO II[75]	THR/ TKR (1,949)	Dab 50-, 150-, 225-mg bid; and 300-mg od Enox 40-mg od	6–10	8.2% Dab 150-mg bid[b] 8.3% Dab 300-mg od[b] 4.6% Enox	4.1% Dab 150-mg bid[b] (p=0.10) 4.7% Dab 300-mg od[b] (p=0.051) 2.0% Enox	NA	4.1% Dab 150-mg bid[b] 4.9% Dab 300-mg od[b] 2.6% Enox	7.9% Dab 150-mg bid[b] 9.6% Dab 300-mg od[b] 6.4% Enox
RE-NOVATE[22]	THR (3,463)	Dab 150-, 220-mg od Enox 40-mg od	28–35	6.0% Dab 150-mg od 6.2% Dab 220-mg od 5.1% Enox	1.3% Dab 150-mg od (p=0.60) 2.0% Dab 220-mg od (p=0.44) 1.6% Enox	NA	4.7% Dab 150-mg od 4.2% Dab 220-mg od 3.5% Enox	6.2% Dab 150-mg od, 6.1% Dab 220-mg od 6.4% Enox
RE-MODEL[23]	TKR (2,076)	Dab 150-, 220-mg od Enox 40-mg od	6–10	8.1% Dab 150-mg od 7.4% Dab 220-mg od 6.6% Enox	1.3% Dab 150-mg od (p=1.0) 1.5% Dab 220-mg od (p=0.82) 1.3% Enox	NA	6.8% Dab 150-mg od 5.9% Dab 220-mg od 5.3% Enox	8.4% Dab 150-mg od 8.8% Dab 220-mg od 9.9% Enox
RE-MOBILIZE[24]	TKR (2,596)	Dab 150-, 220-mg od Enox 30-mg bid	12–15	3.1% Dab 150-mg od 3.3% Dab 220-mg od 3.8% Enox	0.6% Dab 150-mg od 0.6% Dab 220-mg od 1.4% Enox	NA	2.5% Dab 150-mg od 2.7% Dab 220-mg od 2.4% Enox	2.5% Dab 150-mg od 2.7% Dab 220 mg od 2.4% Enox[cd]
Rivaroxaban								
ODIXa-KNEE[76]	TKR (613)	Riv 2.5-, 5-, 10-, 20-, 30-mg bid Enox 30-mg bid	5–9	2.9% Riv 5-mg bid[b] 4.8% Enox	0% Riv 5-mg bid[b] 1.9% Enox (p=NS)	0% Riv 5-mg bid[b] 1.9% Enox	2.9% Riv 5-mg bid[b] 2.9% Enox	5.9% Riv 5-mg bid[b] 2.9% Enox
ODIXa-OD-HIP[77]	THR (845)	Riv 5-, 10-, 20-, 30-, 40-mg od Enox 40-mg od	5–9	2.8% Riv 10-mg od[b] 5.1% Enox	0.7% Riv 10-mg od[b] 1.9% Enox (p=NS)	NA	2.1% Riv 10-mg od[b] 3.2% Enox	3.5% Riv 10-mg od[b] 3.8% Enox
ODIXa-HIP[27]	THR (704)	Riv 2.5-, 5-, 10-, 20-, 30-mg bid Enox 40-mg od	5–9	8.1% Riv 5-mg bid[b] 1.5% Enox	2.2% Riv 5-mg bid[b] 1.5% Enox (p=NS)	2.2% Riv 5-mg bid[b] 0.8% Enox	5.9% Riv 5-mg bid[b] 0% Enox	4.4% Riv 5-mg bid[b] 4.5% Enox
Dose-escalation study[78]	THR (625)	Riv 2.5-, 5-, 10-, 20-, 30-mg bid, and 30-mg od Enox 40 mg od	5–9	3.8% Riv 5-mg bid[b] 1.9% Enox	2.5% Riv 5-mg bid[b] 0% Enox	2.5% Riv 5-mg bid[b] 0% Enox	1.3% Riv 5-mg bid[b] 1.9% Enox	5.0% Riv 4.9% Enox
RECORD1[29]	THR (4,433)	Riv 10-mg od Enox 40-mg od	31–39	3.2% Riv 2.5% Enox	0.3% Riv 0.1% Enox (p=0.18)	NA	2.9% Riv 2.4% Enox	3.2%[d] Riv 3.5%[d] Enox

Table 6: continued

Study	Indication (N)	Regimens	Duration, days	Major/clinically significant bleeding[a]	Major bleeding	Major/surgical site bleeding	Clinically relevant non-major bleeding	Minor bleeding
RECORD2[30]	THR (2,457)	Riv 10-mg od Enox 40-mg od	31–39 Riv 10–14 Enox	3.4% Riv 2.8% Enox	<0.1% Riv <0.1% Enox	NA	3.3% Riv 2.7% Enox	3.5%[d] Riv 2.9%[d] Enox
RECORD3[31]	TKR (2,459)	Riv 10-mg od Enox 40-mg od	10–14	3.3% Riv 2.8% Enox	0.6% Riv 0.5% Enox (p=0 .77)	NA	2.7% Riv 2.3% Enox	1.8%[d] Riv 2.5%[d] Enox
RECORD4[32]	TKR (3,034)	Riv 10-mg od Enox 30-mg bid[e]	10–14	3.0% Riv 2.3% Enox (p=0.1790)	0.7% Riv 0.3% Enox (p=0.1096)	NA	2.6% Riv 2.0% Enox	10.2%[c] Riv 9.2%[c] Enox
RECORD1–3[64]	THR and TKR (9,349)	Riv 10-mg od Enox 40-mg od[e]	10–39	3.3% Riv 2.7% Enox	0.3% Riv 0.2% Enox (p=0.305)	NA	3.0% Riv 2.5% Enox	5.6% Riv 5.3% Enox
FDA pooled analysis of RECORD1–4[33]	THR and TKR (12,383)	Riv 10-mg od Enox 40-mg od or 30-mg bid	10–39	3.19% Riv 2.55% Enox (p=0.04)	0.39% Riv 0.21% Enox (p=0.08)	1.80% Riv 1.37% Enox (p=0.06)	NA	NA
Apixaban								
APROPOS[28]	TKR (1,217)	Apix 5-, 10-, 20-mg od, and 2.5-, 5-, 10-mg bid Enox 30-mg bid or warfarin (INR 1.8–3.0)	10–14	0% Apix 2.5-mg bid[b] 1.3% Enox 0% Warfarin	0% Apix 2.5-mg bid[b] 0% Enox 0% Warfarin	NA	NA	3.9% Apix 2.5-mg bid[b] 4.0% Enox 5.3% Warfarin
ADVANCE-1[34]	TKR (3,184)	Apix 2.5-mg bid Enox 30-mg bid	10–14	2.9% Apix 4.3% Enox (p=0.03)	0.7% Apix 1.4% Enox (p=0.05)	0.5% Apix 0.9% Enox	2.2% Apix 3.0% Enox	2.4% Apix 2.5% Enox
ADVANCE-2[35]	TKR (3,009)	Apix 2.5-mg bid Enox 40-mg od	10–14	3.5% Apix 4.8% Enox (p=0.0881)	0.6% Apix 0.9% Enox (p=0.3014)	0.5% Apix 0.7% Enox	2.9% Apix 3.8% Enox (p=0.1668)	3.4% Apix 3.6% Enox
ADVANCE-3[36]	THR (5,332)	Apix 2.5-mg bid Enox 40-mg od		4.8% Apix 5.0% Enox (p=0.72)	0.8% Apix 0.7% Enox (p=0.54)	0.7% Apix 0.6% Enox	4.1% Apix 4.5% Enox (p=0.43)	6.9% Apix 7.5% Enox

[a]Major bleeding rates cited for the RECORD trials exclude haemorrhagic surgical wound complications. [b]Dose most similar to the dose(s) selected for the phase III program. [c]Values refer to any non-major bleeding. [d]Values refer to non-major bleeding, excluding clinically significant bleeding, excessive wound haematoma, and reported surgical site bleeding. [e]The dose regimen for enoxaparin used in RECORD4 is not an approved dose regimen of enoxaparin for prophylaxis of deep-vein thrombosis in patients undergoing TKR in the United States. Dab, dabigatran etexilate; bid, twice daily; od, once daily; NA, not available; Enox, enoxaparin; Riv, rivaroxaban; NS, not significant; Apix, apixaban; INR, international normalised ratio; TKR, total knee replacement.

An overview of the reported data on bleeding in clinical trials involving new oral anticoagulants is included below. It is important to emphasise that: enoxaparin is used in almost all recent trials as the standard comparator, phase II trials involve escalating doses of the study drug whereas the dose of enoxaparin remains constant in the different patient groups, and the definition of bleeding or clinically relevant bleeding is variable among different trials (74). In the large phase II dosing trial (BISTRO II) in patients undergoing THR or TKR (n=1,949), major bleeding episodes were significantly higher in patients receiving dabigatran 150-mg and 225-mg twice daily and 300-mg once daily compared with dabigatran 50-mg twice daily (p<0.05) (75). Compared with enoxaparin 40-mg once daily, major bleeding was lower in the dabigatran 50-mg twice-daily group (2.0% vs. 0.3%, respectively; p=0.047). A trend for increased bleeding was observed in patients receiving dabigatran 150-mg twice daily (4.1% vs. 2.0%; p=0.10), 225-mg twice daily (3.8% vs. 2.0%; p = 0.15), and 300 mg once daily (4.7% vs. 2.0%; p=0.051) compared with enoxaparin (▶Table 6) (21–24, 27–34, 64, 75–78). Three large phase III studies compared once-daily dabigatran 150 mg and 220 mg with once daily enoxaparin 40 mg (RE-NOVATE and RE-MODEL) and enoxaparin 30 mg twice daily (RE-MOBILIZE) in patients undergoing THR and TKR. Major bleeding rates were relatively low and were not significantly different among all of the groups (▶Table 6) (22–24).

In the phase II dose-escalation study in patients following THR (n=625) there was a significant dose-response relationship between rivaroxaban and major bleeding (p=0.0008) and a tendency towards higher rates of clinically-relevant, non-major bleeding and minor bleeding with higher rivaroxaban doses (▶Table 6) (78). The four RECORD trials (29–32), compared rivaroxaban with enoxaparin in THR or TKR patients. The duration of prophylaxis and the enoxaparin dosing were not consistent. Some of the trials also used dosing regimens different from recommended protocols in US practice. In RECORD2 enoxaparin was administered for a mean duration of 12.4 days whereas rivaroxaban was given for 33.5 days (30). In RECORD3 enoxaparin 40-mg once daily was the comparator instead of enoxaparin 30-mg twice daily (31). Moreover, surgical site bleeding was not included in the major bleeding category in the RECORD trial data submitted for review (33). In the FDA-integrated analysis of the pooled RECORD trial data comparing rivaroxaban (n=6,183) with enoxaparin (n=6,200), there was more major bleeding in the rivaroxaban-treated patients (0.39% vs. 0.21% with enoxaparin; p=0.076 time to first event; p=0.05 time to multiple event). There were also more major bleeding plus surgical site bleeding events (1.80% vs. 1.37%; p=0.06 time to first event; p=0.05 time to multiple event). Furthermore, there were more major or non-major clinically relevant bleeding events (3.19% with rivaroxaban vs. 2.55% with enoxaparin; p=0.039 time to first event; p=0.02 time to multiple event) (33).

Drug-drug interactions with concomitant administration of certain medications may also increase the risk of bleeding. Limited data have demonstrated a prolongation of bleeding time with concomitant rivaroxaban and clopidogrel therapy even though clopidogrel does not alter rivaroxaban pharmacokinetics (16, 79). In the ATLAS-TIMI 46 trial, rivaroxaban 5 mg to 20 mg was studied in combination with aspirin, with or without thienopyridine in patients with acute coronary syndromes (80). Rivaroxaban was associated with a dose-dependent increase in clinically significant bleeding compared with placebo (p<0.0001). To permit downward titration in special patient populations at-risk for potential higher rivaroxaban drug exposure, the FDA has requested that a tablet of a dose lower than 10 mg be manufactured (33).

In the phase II APROPOS study in patients undergoing TKR (n=1,217), the incidence of major bleeding ranged from 0% with apixaban 2.5-mg twice daily to 3.3% with apixaban 20-mg once daily. There was no major bleeding observed in the enoxaparin 30 mg-twice-daily group or in the adjusted-dose warfarin group (target international normalised ratio of 1.8–3.0) (28). A significant dose-related increase in the incidence of total adjudicated bleeding events was noted in the apixaban 20-mg once-daily (p=0.01) and 2.5-mg twice-daily groups (p=0.02). In the phase III ADVANCE-1 trial (n=3,184), major and clinically-relevant non-major bleeding events were reported in 2.9% of patients receiving apixaban 2.5 mg twice-daily and in 4.3% of patients receiving enoxaparin 30-mg twice daily (p=0.03) (34). In the ADVANCE-2 trial (n=3,009), adjudicated major and clinically-relevant non-major bleeding events occurred in 3.5% of patients receiving apixaban 2.5 mg twice-daily and 4.8% of patients receiving enoxaparin 40-mg once daily (35). In the recently published ADVANCE-3 trial (n=5,332), rates of adjudicated major and clinically-relevant non-major bleeding events were similar in both the apixaban and enoxaparin groups (4.8% vs. 5.0%, respectively) (36).

In the APPRAISE trial (n=1,715) patients with acute coronary syndromes were randomised to receive one of four doses of apixaban or placebo plus aspirin, with or without clopidogrel (46). Following reports of excess total bleeding, the two higher-dose apixaban groups (10-mg twice daily and 20-mg once daily) were prematurely discontinued. The rate of total bleeding reported in these groups were 24.2% and 23.9%, respectively, compared with 6.1% with placebo. Overall, the risk of major or clinically relevant non-major bleeding was higher with apixaban 2.5-mg twice daily (5.7%; 95% CI 3.4–8.9) and 10-mg once daily (7.9%; 95% CI 5.2–11.5) than with placebo (3%; 95% CI 1.8–4.7). In addition, increases in bleeding events were more apparent in patients also receiving clopidogrel. Major bleeding occurred in 2.2% of patients receiving apixaban 2.5-mg once daily plus clopidogrel, but in no patients receiving apixaban with no clopidogrel (46). It is important to emphasise that these data were in non-surgical patients. Potential adverse events may be even greater in surgical patients.

Community clinical practice data

At present there are no reported or published data regarding the efficacy and safety of the new oral anticoagulants in 'real world' community clinical practices. Most of the patients who participated in the clinical trials represent a selected population with pre-specified inclusion and exclusion criteria. Many patients with co-morbidities, those at risk of bleeding, renal impairment, or liver abnormalities were excluded. It is important that studies are performed in large patient populations with diverse medical co-morbidities, taking multiple drugs, with various cardiac profiles, renal function variations, and in those undergoing orthopaedic surgeries using different surgical and anaesthesia techniques.

Conclusions

The ideal anticoagulant does not yet exist. The new oral anticoagulants have the potential to improve VTE prophylaxis and treatment practices with a convenient mode of administration and reduced monitoring for both physicians and patients (81). These newer agents include factor Xa inhibitors rivaroxaban and apixaban and the oral direct thrombin inhibitor dabigatran. Dabigatran and rivaroxaban have been demonstrated to be efficacious and safe in multiple large clinical trials. However, there are still several safety issues regarding the use of these new oral anticoagulants in 'real-world' clinical practice.

Bleeding complications are the major concern with any anticoagulant and it is the single most important reason given by US orthopaedic surgeons when responding to why they have changed

the pharmacological prophylaxis protocol in their patients. Safety outcomes are very difficult to interpret and compare between the different agents across different clinical trial designs. This is mainly due to the broad range of definitions of bleeding complications used in each specific clinical trial, which can influence the apparent safety profile of each drug and may lead to underestimation of bleeding risk (74). In addition, any meta-analysis is limited by the heterogeneity of patient populations, inclusion and exclusion criteria, and dosing regimens for both the study drug and the comparator. It is essential that drug-drug and drug-food interactions are further characterised as these can potentially have a substantial effect on the bleeding risks. At present, dabigatran and rivaroxaban are both approved for use outside of the United States for thromboprophylaxis in patients undergoing THR and TKR. Dabigatran is approved in the United States for a non-orthopaedic indication (non-valvular atrial fibrillation). Rivaroxaban was reviewed by the US FDA in spring 2009. However, the FDA has delayed approval and requested additional clinical safety information from the developers.

Continuous surveillance must be undertaken when the new oral anticoagulants are extended to 'real-world' community clinical practice. It is especially important to monitor any potential rebound effects that could result in more complications beyond the short-term use.

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Conflict of interest

Dr. Huo is a consultant for Boehringer Ingelheim, Genzyme, Stryker and DePuy.

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