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The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery

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Abstract

Venous thromboembolism is a common cause of morbidity and mortality among patients undergoing elective orthopedic surgery. Due to the high incidence of venous thromboembolism in this setting, perioperative anticoagulation is the recommended approach for thromboprophylaxis. Low molecular weight heparin (LMWH), fondaparinux and warfarin are the agents commonly used for thromboprophylaxis. The well-recognized limitations of warfarin and the inconvenience and discomfort associated with the subcutaneous administration of low molecular weight heparin and fondaparinux inspired intense investigation to develop novel oral anticoagulants (NOACs) with more predictable pharmacokinetics, fewer drug interactions and no need for regular laboratory monitoring. Three NOACs have been demonstrated to be effective for thromboprophylaxis after total hip arthroplasty (THA) and total knee arthroplasty (TKA) in large randomized controlled trials. Here we review the pharmacology of rivaroxaban, dabigatran, and apixaban, summarize the major clinical trials of these agents in thromboprophylaxis after THA

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and TKA, and discuss the clinical factors to be considered by providers when selecting a NOAC for their patients.

Keywords

anticoagulants; apixaban; arthroplasty; dabigatran; hip; knee; orthopedic; prophylaxis; replacement; rivaroxaban; venous thromboembolism

Venous thromboembolism (VTE) is a major contributor to morbidity and mortality among orthopedic patients. In the absence of pharmacologic prophylaxis, the incidence of deep venous thrombosis (DVT) among patients undergoing total hip arthroplasty (THA) is 40–60%, of which 2–5% are symptomatic [1,2]. Similarly, the incidence of VTE among patients undergoing total knee arthroplasty (TKA) without prophylactic anticoagulation is as high as 85% [1,2]. With contemporary VTE prophylaxis, 1.1% of patients undergoing TKA and 0.5% of patients undergoing THA will suffer VTE before hospital discharge [3]. In a single-center observational cohort study, Lapidus *et al.* found that 3.7% of patients undergoing TKA suffered post-operative VTE (DVT 3.6% and pulmonary embolism (PE) 0.2%) within 6 weeks compared with 2% of THA patients (DVT 1.3% and PE 0.7%) [4]. Consequently, orthopedic surgeons face the dual challenge of preventing potentially life-threatening thromboembolism while at the same time trying to avoid bleeding complications in patients with diverse comorbidities and wide age ranges. In addition to the economic burden such complications impose, their toll is immense on the patient's health status and quality of life. VTE increases a patients' stay in the intensive care unit by 10-fold, doubles the hospital length of stay and almost doubles the cost of their inpatient care [5]. With significant financial pressures to reduce the length of hospital stay, many VTE occur after hospital discharge. A recent observational study from Sweden noted that 85% of DVT and 80% of PE were diagnosed after hospital discharge. These data underscore the importance of post-discharge prophylaxis to prevention of VTE [4].

Pharmacologic thromboprophylaxis plays a major role in reducing the morbidity and mortality of VTE. For years, clinicians' choices for anticoagulant thromboprophylaxis were limited to unfractionated or low molecular weight heparin (LMWH), fondaparinux and warfarin. The need for parenteral administration and laboratory monitoring, and the concerns over numerous drug–drug and drug–food interactions have stimulated intense interest in alternative oral anticoagulants for thromboprophylaxis and treatment of VTE. Improved understanding of the molecular structure of the serine protease coagulation factors has led to the development of a growing list of novel oral anticoagulants (NOACs). Orthopedic surgeons are likely to encounter patients on NOACs as these agents gain the US FDA approval for an increasing number of indications.

In this review, we will review the pharmacology and the major clinical trials of the three most widely studied NOACs (rivaroxaban, dabigatran and apixaban), and discuss the perioperative management of these agents in orthopedic patients.

Thrombin formation & its role in VTE

A well-regulated system exists *in vivo* to balance pro- and anticoagulant factors preventing unwarranted intravascular thrombin formation. The hemostatic system relies on targeted activation of the coagulation cascade at sites of vascular injury in the extravascular compartment to prevent bleeding. The primary regulator for the initiation of this process is tissue factor (TF). This molecule is primarily located at extravascular sites and initiates a sequence of events leading to the assembly of the prothrombinase complex (activated factors X and V) on the surface of activated platelets to convert prothrombin to thrombin [6]. Thrombin then transforms fibrinogen into fibrin, which polymerizes to produce a protease-resistant fibrin gel (Figure 1). Since activated factor X (FXa) and thrombin play a pivotal role in this process, development and testing of direct inhibitors of these critical proteases has been an area of intense investigation [7].

Limitations of traditional anticoagulants

Warfarin

Warfarin has traditionally been the mainstay of long-term anticoagulation therapy. It inhibits vitamin K epoxide reductase; a key enzyme responsible for recycling vitamin K, an essential cofactor for the production of gamma-carboxy-glutamic acid residues necessary for factors II, VII, IX, X, proteins C and S to bind to phospholipid-rich cell membranes [8]. In the absence of these post-translational modifications, the vitamin K-dependent coagulation factors cannot function effectively as serine pro-teases, thus inhibiting the formation of fibrin clot. Since warfarin does not act as a direct inhibitor of coagulation proteins, patients must be on warfarin for at least 5 days before therapeutic anticoagulation is achieved [8]. This time reflects the time required for the functional levels of the various vitamin K-dependent factors to decline in accordance with their half-lives.

For years, warfarin has been the only oral anticoagulant used for thromboprophylaxis. Although effective, warfarin has numerous limitations including substantial variability in individual dose requirements (more than 100-fold from 0.5 to 70 mg daily), the need for regular laboratory monitoring, a long half-life, as well as significant drug–drug and drug–diet interactions [9].

Unfractionated & low molecular weight heparin

Unfractionated heparin (UFH) and LMWH function as anticoagulants by binding to antithrombin (AT) and accelerating the kinetics of its inhibitory activity against the serine proteases thrombin and factor Xa as well as factors IXa, XIa, and XIIa [10,11]. Heparin is a collection of sulfated mucopolysaccharides of molecular weights varying from 6000 to 20,000 Da that is principally derived from porcine intestines [12]. Due to its larger size, thrombin can be inhibited only by higher molecular weight fractions of heparin in conjunction with AT. Conversely, factor Xa inhibition can be catalyzed by low or high molecular fractions of heparin [10,11]. Therefore, UFH can accelerate AT-mediated inhibition of both thrombin and factor Xa while LMWH promotes primarily factor Xa inhibition given its shorter polysaccharide chain lengths [10,11].

UFH and LMWH can be administered either intravenously or subcutaneously, which makes them less desirable for out-of-hospital use. Due to more extensive binding to cell membranes and proteins, UFH is usually monitored using the activated partial thromboplastin time (aPTT) to ensure therapeutic levels are maintained. LMWH is generally administered subcutaneously without monitoring for both prophylactic and therapeutic indications. Since it is eliminated primarily by the kidneys, LMWH must be dose-reduced or avoided in patients with renal failure depending upon its severity [13]. UFH is associated with heparin-induced thrombocytopenia (HIT), an antibody-mediated prothrombotic syndrome. Although the risk is 10-fold greater with UFH, LMWH is also associated with HIT, though not typically at prophylactic doses [14–16].

Fondaparinux

Fondaparinux is a synthetic polysaccharide parenteral anticoagulant derived from the five sugar residues that bind to the heparin-binding site on AT [17]. Due to its small size, fondaparinux only catalyzes AT-mediated inhibition of factor Xa. Fondaparinux is administered subcutaneously in fixed doses for the prevention and treatment of VTE. The drug has a long half-life (17–21 h with normal renal function), is exclusively excreted by the kidneys and has no available antidote, so it should be used with considerable caution in patients with a creatinine clearance (CrCl) less than 30 ml/min [18]. Like UFH and LMWH, fondaparinux is administered parenterally, so its use outside the hospital is less desirable. Unlike UFH and LMWH, fondaparinux has been associated very rarely with HIT and has been used in a number of cases to treat HIT [19]. Unlike the NOACs, fondaparinux is approved for VTE prophylaxis in patients undergoing hip fracture surgery.

Novel oral anticoagulants

The ideal anticoagulant should be orally administered, be inexpensive, target a single enzyme in the coagulation cascade, require no monitoring, have minimal drug–drug and drug–diet interactions, not cause thrombocytopenia and have a low risk of bleeding. The development of NOACs has focused on inhibiting thrombin and factor Xa given their central role in the coagulation cascade. Compared with heparin where steric hindrance prevents the heparin–ATIII complex from inactivating fibrin-bound thrombin, target-specific, small molecule, direct thrombin inhibitors have the advantage of inhibiting free and clot-bound thrombin [20]. Therefore, direct thrombin inhibitors could be more effective in prevention of thrombus extension and re-thrombosis [20]. Similarly, direct factor Xa small molecule inhibitors can inhibit both free and prothrombinase-bound FXa, and eventually clot-associated FXa. The extended capabilities of these small molecular inhibitors would prevent all forms of factor Xa from activating prothrombin, thus inhibiting thrombin generation and clot propagation [21,22].

Rivaroxaban

Pharmacology of rivaroxaban

Rivaroxaban (Xarelto®) is an oxazolidinone derivative that is an oral, direct, reversible and selective inhibitor of FXa, both in its free and prothrombin-bound forms [23–25]. Although, the PT may be useful for a rough estimate regarding the presence of the rivaroxaban in

plasma depending upon the reagent used, calibrated chromogenic factor Xa inhibition assays are the most accurate method for measuring rivaroxaban [26–28].

In a study conducted on 108 healthy white males, rivaroxaban was safe in doses up to 80 mg [27]. Maximum FXa activity inhibition after tablet administration was observed within 1–4 h with all the doses tested in the study, with a half-life of 5–9 h. Both PT and aPTT are prolonged in a dose-dependent fashion but the degree of prolongation varies depending upon the reagent used to perform the test. PT and aPTT prolongation paralleled FXa inhibition profiles. At a single dose of 10 mg, the dosage used in subsequent clinical thromboprophylaxis trials, the PT increased by 1.4-times and aPTT by 1.3-times at 2 h. The HepTest, a clot-based anti-FXa assay, in turn increased up to 1.9-times. Thrombin and AT activities, expectedly, were not affected by rivaroxaban [27].

The effects of food, antacids and H₂ antagonists on rivaroxaban were also assessed in a separate study. Food delayed the time to maximum concentration by 1.25 h, and the time to maximum PT by 0.5–1.5 h. Moreover, presence of food increased the maximum PT prolongation from 44 to 53% [29]. Nonetheless, the manufacturer states that the drug may be taken with or without food, as the pharmacokinetic changes are clinically insignificant [101]. On the other hand, antacid or H₂ blocker administration had no effect on either the maximum concentration or PT prolongation [29].

Rivaroxaban pharmacological properties have also been examined in relation to body weight extremes [30], and it showed a 15% increase in PT prolongation. This effect was considered clinically insignificant, and the study concluded that no dose adjustment is required in patients <50 or >120 kg.

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2 and P-glycoprotein (P-gp). Inhibitors and inducers of these enzymes can affect the level of rivaroxaban [101]. Some of the commonly used combined P-gp and CYP3A4 inhibitors include ketoconazole, amiodarone, verapamil, ritonavir, clarithromycin and fluconazole, and they can cause increased exposure and side effects, of rivaroxaban [101]. On the other hand, combined P-gp and CYP3A4 inducers such as rifampicin, carbamazepine and phenytoin can cause decreased rivaroxaban exposure and hence may decrease its efficacy [101].

Summary of phase III clinical trials of rivaroxaban in thromboprophylaxis after elective major orthopedic surgery—Rivaroxaban is approved in the European Union and the USA for VTE prophylaxis in patients undergoing elective hip or knee replacement surgery [31]. The RECORD program compared rivaroxaban with enoxaparin in a series of four randomized, double-blind Phase III trials that included more than 12,500 patients and showed that rivaroxaban was superior to enoxaparin in thromboprophylaxis after TKA or THA, with a similar safety profile (Table 1) [31]. The primary efficacy outcome in all the RECORD trials was a composite of DVT (symptomatic or venographically detected), non-fatal PE or all-cause mortality, while the main secondary efficacy outcome was the rate of major VTE (proximal DVT, non-fatal PE or death from VTE). The primary safety outcome was major bleeding which was defined as fatal bleeding; bleeding into a critical organ or bleeding requiring re-operation or extra-surgical site bleeding that was clinically overt and

was associated with a fall in the hemoglobin level of ≥ 2 g/dl or required transfusion of ≥ 2 units of whole blood or packed cells up to 2 days after last dose.

RECORD1 trial: In RECORD1, a randomized, double-blind, double-dummy study, 4500 patients undergoing THA were allocated to receive 10 mg of rivaroxaban once daily starting after surgery or 40 mg once daily of enoxaparin starting the evening before the operation [32]. The primary efficacy outcome occurred in 1.1% of patients in the rivaroxaban group and 3.7% in the enoxaparin group (absolute risk reduction [RR]: 2.6%; 95% CI: 1.5–3.7%; $p = 0.001$) [32]. The incidence of major VTE was significantly lower in the rivaroxaban group (0.2%) versus the enoxaparin group (2%) ($p = 0.001$). Therefore, the incidence of the primary efficacy outcome was 70% lower with rivaroxaban and the incidence of major VTE was 90% lower [32]. Non-fatal PE occurred at a rate of 0.3% in the rivaroxaban arm and at 0.1% in the enoxaparin group ($p = 0.37$). Major bleeding was higher with rivaroxaban (0.3 vs 0.1%), though not reaching statistical significance, while the risk of any on-treatment bleeding was almost the same (6.0 vs 5.9%) [32]. There were no significant differences in the rates of cardiovascular events or the liver enzyme abnormalities between the two arms [32].

RECORD2 trial: RECORD2 was an extended prophylaxis study that compared extended duration rivaroxaban with short-term enoxaparin for the prevention of VTE after THA [33]. A once-daily 10 mg dose of rivaroxaban for 31–39 days was compared with enoxaparin 40 mg once daily for 10–14 days. The primary efficacy outcome occurred in 2.0% of those enrolled in the rivaroxaban group and 9.3% of those enrolled in the enoxaparin group (absolute RR: 7.3%; 95% CI: 5.2–9.4; $p = 0.001$) [33]. Major VTE was also significantly lower with rivaroxaban (0.6 vs 5.1%) [33]. Non-fatal PE occurred in 0.1% of patients on rivaroxaban and in 0.5% of patients on enoxaparin ($p = 0.37$). Nonetheless, the efficacy comparisons should be taken with caution, as the two prophylaxis arms were significantly different in duration. Major bleeding rates were similar between the two arms (6.6% in the rivaroxaban arm and 5.5% in the enoxaparin group, $p = 0.25$) [33].

RECORD3 trial: The RECORD3 study evaluated TKA patients, in a randomized, double-blind trial comparing rivaroxaban 10 mg once daily (beginning 6–8 h after surgery) versus enoxaparin 40 mg once daily (beginning 12 h before surgery) for 10–14 days [34]. The primary efficacy outcome in the rivaroxaban arm was 9.6% and that in the enoxaparin arm was 18.9% ($p = 0.001$). Major and symptomatic VTE events also were significantly lower with rivaroxaban. The PE incidence was 0% with rivaroxaban and 0.45% with enoxaparin, which was not statistically different. The difference in major or any bleeding was statistically insignificant [34].

RECORD4 trial: As with RECORD3, RECORD4 showed a significant reduction in thrombotic events in TKA patients receiving 10 mg rivaroxaban compared with enoxaparin 30 mg every 12 h for 10–14 days [35]. Enoxaparin was given according to the US dosing regimen and started 12–24 h post-operatively. The primary efficacy outcome occurred in 6.9% of patients on rivaroxaban and 10.1% of patients on enoxaparin ($p = 0.0118$) [35]. PE occurred in 5 of 1526 in the rivaroxaban arm and 8 of 1508 in the enoxaparin arm ($p =$

0.5250). There was no significant difference in major bleeding between rivaroxaban (0.7%) and enoxaparin (0.3%) ($p = 0.11$) [35].

Summary of the RECORD program—The RECORD program concluded that rivaroxaban was more efficacious than enoxaparin for thromboprophylaxis after TKA or THA, and provided a similar safety profile [36]. A pooled analysis of data from these studies showed that rivaroxaban was more effective than enoxaparin in reducing the incidence of the composite of symptomatic VTE and all-cause mortality at 2 weeks and at the end of the planned medication period [37]. The rate of major bleeding was similar at 2 weeks and at the end of the planned medication period [37]. Other meta-analyses, however, suggested that rivaroxaban was associated with a significantly increased risk of bleeding compared with enoxaparin, despite achieving better thromboprophylaxis [38,39].

Despite recruiting large number of patients, the aforementioned Phase III trials had the limitation of excluding a large number of patients from the primary efficacy analysis due to the invalid assessments of thromboembolism using bilateral venography [36]. Currently, the XAMOS trial (Xarelto in the prophylaxis of post-surgical VTE after elective major orthopedic surgery of hip or knee) is under way and will evaluate the effectiveness and safety of rivaroxaban versus standard of care in 15,000 patients at 200 centers worldwide [40].

Reversal of rivaroxaban

There is currently no approved antidote for rivaroxaban, although one agent is under active investigation (56) [41–45]. r-Antidote (PRT064445) (Portola Pharmaceuticals, Inc. South San Francisco, CA, USA) is a genetically engineered inactivated form of factor Xa that tightly binds direct (rivaroxaban, apixaban, etc.) and indirect (fondaparinux, LMWHs) factor Xa inhibitors. Recently published results of *in vivo* animal studies and *in vitro* human volunteer studies appear promising [45]. At the current time, in the event of major bleeding, standard treatment strategies include delaying the next dose, mechanical compression, fluid replacement and/or surgical intervention. Preclinical studies have demonstrated the efficacy of recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrate (aPCC) in normalizing hemostatic parameters in cases of rivaroxaban overdose [42–44]. In addition, an *in vitro* study evaluating rivaroxaban reversal (along with dabigatran reversal) showed that, in the case of rivaroxaban, the aPCC FEIBA[®] (Factor VIII Inhibitor Bypassing Activity) corrected all quantitative and kinetic parameters affected by rivaroxaban, compared with PCC and rFVIIa which only corrected certain investigational parameters [41]. Hemodialysis, which can rapidly reduce dabigatran levels, is not effective for rivaroxaban, which is highly protein-bound.

Dabigatran etexilate

Pharmacology of dabigatran etexilate

Dabigatran etexilate (Pradaxa[®]) is an orally active pro-drug that is rapidly converted to the active direct thrombin inhibitor, dabigatran [46]. Given the important role thrombin plays in platelet aggregation and activation, dabigatran also prevents platelet aggregation in a dose-

dependent fashion [47]. Upon oral administration, dabigatran etexilate is rapidly absorbed and metabolized to the active form dabigatran, with the latter's maximum plasma concentration attained after 2 h [48–50]. After that, dabigatran concentration drops biphasically. It reaches less than 30% within 4–6 h, and then gets eliminated with a half-life of 12–17 h [21]. Dabigatran is renally excreted. Hence, severe renal impairment increases dabigatran's peak plasma concentration up to 2.4-times, and the half-life to approximately 27 h [49,50].

Dabigatran etexilate's absorption from enterocytes is facilitated by P-gp, so P-gp inducers or inhibitors can affect dabigatran etexilate's absorption [51]. Plasma levels of the drug are increased in the presence of P-gp inhibitors such as quinidine, verapamil, dronedarone, ketoconazole and amiodarone. P-gp inducers like rifampin, carbamazepine and phenytoin decrease dabigatran's plasma levels [51]. Dabigatran is not significantly metabolized by any cytochrome P450 enzyme, nor is it an inducer or an inhibitor of these enzymes. However, 20% of dabigatran is conjugated with glucuronosyl transferases to the fully pharmacologically active glucuronide forms [52]. By contrast, renal excretion constitutes more than 80% of the clearance of this drug. As for protein displacement interaction with other drugs, only 35% of the drug is bound to albumin, making the effect of such interactions on pharmacokinetics or pharmacodynamics unlikely [52].

Dabigatran results in prolongation of the aPTT [50], but this relationship is not linear, so the aPTT cannot be used to monitor dabigatran levels [53]. The Hemoclot thrombin inhibitor test, a diluted thrombin time assay enabling the accurate determination of dabigatran plasma concentrations, is the most sensitive assay for dabigatran that can be used for laboratory monitoring [50]. Dabigatran also prolongs the ecarin clotting time (ECT), a measure of thrombin clotting using a snake venom derivative to generate a prothrombin intermediate, in a dose-dependent manner, and ECT may be a more appropriate test for monitoring dabigatran activity [54]. Like other NOACs, dabigatran prolongs PT, but PT measures are variable across different doses, making PT an inappropriate clot-based assay for dabigatran [54].

Summary of phase III clinical trials of dabigatran etexilate in thromboprophylaxis after elective major orthopedic surgery

Dabigatran has completed phase III clinical trials in Europe and the USA to evaluate its potential in thromboembolic disorders. It was approved by the EMA for primary prevention of VTE in adult patients who have undergone elective hip or knee replacement in 2008, and has been subsequently launched for this indication in more than 100 countries [55]. Table 2 lists phase III trials that evaluated dabigatran etexilate for thromboprophylaxis after elective major orthopedic surgery. The primary efficacy outcome in all the trials was a composite of DVT (symptomatic or venographically detected), non-fatal PE or all-cause mortality, while the main secondary efficacy outcome was the rate of major VTE (proximal DVT, non-fatal PE or death from VTE). The primary safety outcome was major bleeding which was defined as fatal bleeding; bleeding into a critical organ or bleeding requiring re-operation or extra-surgical site bleeding that was clinically overt and was associated with a fall in the

hemoglobin level of ≥ 2 g/dl or required transfusion of ≥ 2 units of whole blood or packed cells up to 2 days after last dose.

RE-NOVATE trial—This was a phase III trial evaluating about 3500 patients undergoing THA who were randomized to treatment for 28–35 days with either dabigatran etexilate (220 mg once daily or 150 mg once daily) or enoxaparin 40 mg once daily [56]. Both dabigatran doses proved non-inferior to enoxaparin for total VTE and all-cause mortality. Moreover, there was no significant difference in major bleeding rates with either dose of dabigatran etexilate compared with enoxaparin [56]. The frequency of increased liver transaminases and of acute coronary events during the study did not differ significantly between the groups [56]. The study concluded that oral dabigatran etexilate was as effective as enoxaparin in reducing the risk of VTE after THA, with a similar safety profile [56].

RE-NOVATE II trial—The RE-NOVATE study's results were confirmed in the RENOVATE II study, which showed that extended prophylaxis (28–35 days) with oral dabigatran 220 mg once-daily was as effective as subcutaneous enoxaparin 40 mg once daily in reducing the risk of VTE after THA, and superior to enoxaparin for reducing the risk of major VTE (proximal DVT or non-fatal PE) and VTE-related mortality (2.2 vs 4.2%; $p = 0.03$) during treatment period, with a similar risk of bleeding and safety profiles [57]. The frequency of increased alanine transaminase (ALT) did not significantly differ between the two groups (3.8% in the dabigatran group vs 5.6% in the enoxaparin group; p -value not reported). The frequency of myocardial infarction during the study also did not differ significantly between the groups ($<0.1\%$ in both arms) [57]. The study concluded that oral dabigatran etexilate was as effective as enoxaparin in reducing the risk of VTE after THA, with a similar safety profile [57].

RE-MODEL trial—In another phase III study, RE-MODEL, oral dabigatran etexilate was compared with subcutaneous enoxaparin for the prevention of VTE after TKA [58]. Upon a 6- to 10-day follow-up for VTE and all-cause mortality, 150 and 220 mg once-daily dabigatran doses, started half-dose 1–4 h after surgery, proved to be non-inferior to enoxaparin 40 mg once daily started the evening before surgery. Both drugs were administered for 6–10 days [58]. The incidence of major bleeding, liver enzyme elevation and acute coronary events were comparable among all three treatment groups [58]. *RE-MODEL* concluded that dabigatran etexilate (220 or 150 mg) was at least as effective as enoxaparin and had a similar safety profile for VTE prevention after TKA [58].

RE-MOBILIZE trial—In the RE-MOBILIZE study, conducted on TKA patients, 12–15 days of dabigatran (110 or 220 mg once daily, started 6–12 h post-operatively) was inferior to the North American regimen of subcutaneous enoxaparin 30 mg twice daily for 12–15 days (starting 12–24 h post-operatively) [59]. The VTE rates in the dabigatran arms (31% for the 220 mg once-daily arm and 34% for the 150 mg once-daily dosing) were higher than that in the enoxaparin arm (25%, p -values vs enoxaparin, 0.02 and <0.001 , respectively). Enoxaparin was associated with a statistically insignificant increase in major bleeding rates [59]. The greater intensity of the enoxaparin regimen, delayed starting time of dabigatran (6–12 h post-operatively vs 1–4 h in the RE-MODEL study), and the duration of prophylaxis

may have contributed to the reduced efficacy results in this trial [60]. The proportion of patients with an ALT greater than three-times the upper limit of normal during the study was similar across the study arms, and neither hepatitis nor hepatotoxicity was considered a serious adverse event [59]. Cardiac serious adverse event rates were similar across the study arms and occurred in 9 patients on dabigatran 220 mg once daily, 10 patients on dabigatran 110 mg once daily and 9 patients on enoxaparin 30 mg twice daily [59].

Meta-analyses

A meta-analysis published in 2009 evaluated the combined results of the RE-MODEL and RE-NOVATE trials, which compared the safety and efficacy of 220 mg once daily of dabigatran etexilate and enoxaparin 40 mg once daily for VTE prophylaxis after TKA and THA [61]. The meta-analysis also included the RE-MOBILIZE study, which compared the efficacy and safety of the same dose of dabigatran compared with enoxaparin 30 mg twice daily after TKA [61]. No significant differences were detected between dabigatran and enoxaparin in any end point analyzed, including total VTE and all-cause mortality [61]. The RE-MODEL and RE-NOVATE meta-analysis supported the conclusions of the individual trials that dabigatran is non-inferior to enoxaparin 40 mg once daily, with a similar safety profile, and that of all three trials found no significant differences between treatments in any of the end points analyzed, although, according to the authors, heterogeneity between the trials cannot be ruled out [61]. A pooled analysis of the RE-MOBILIZE, RE-MODEL and RE-NOVATE trials was published in 2010 and showed that both doses of dabigatran were similar to enoxaparin in terms of the composite outcome of major VTE and VTE-related mortality as well as major bleeding risk [62]. Similarly, another pooled analysis of six phase III randomized trials showed that enoxaparin and dabigatran were associated with a similar risk of bleeding and symptomatic VTE plus all-cause mortality [38].

Reversal of dabigatran

A study of normal human volunteers taking dabigatran 150 mg twice daily for 2 days found that a four-factor prothrombin complex concentrate (PCC) could not reverse the anticoagulant activity of dabigatran as measured by the aPTT, thrombin time, endogenous thrombin potential and ECT [41]. By contrast, a four-factor PCC was shown to reduce blood loss and the bleeding time in a rabbit kidney model [53]. The clinical efficacy of factor concentrates such as PCC, aPCC and recombinant human factor VIIa in reversing the anticoagulant effects of dabigatran remain uncertain, as most case reports have employed multiple reversal strategies [63,64]. Hemodialysis appears to be the most effective means to rapidly reduce dabigatran levels [63]. aDabi-Fab, an investigational antibody fragment that binds dabigatran, has been shown to successfully reverse dabigatran anticoagulation *in vivo* in rats and *in vitro* using human plasma [65]. Until this antidote is available, patients with life-threatening bleeding associated with dabigatran should be treated in a multimodality fashion with local hemostatic measures, consideration for transfusion of pro-coagulant blood products (e.g., activated PCC FEIBA, non-activated three- and four-factor PCCs and recombinant activated factor VIIa) and the use of hemodialysis (which can eliminate 60% of the drug within 2–3 h) [60].

Apixaban

Pharmacology of apixaban

Apixaban (Eliquis) is an oral, direct and highly selective pyrazole-based FXa inhibitor that can be used for the prevention and treatment of thromboembolic diseases [31,46]. Like rivaroxaban, apixaban binds both free and prothrombin-bound FXa [31]. It binds directly to the active site of FXa without requiring AT [31]. Apixaban is rapidly absorbed after oral administration, typically reaching maximal plasma concentration within 1–3.5 h [66,67]. The drug typically reaches steady state within 3 days, and has a half-life of about 12 h [67,68].

Apixaban is a substrate for P-gp and is metabolized mainly by CYP3A4/5, although other enzymes, particularly CYP1A2 and CYP2J2, play a minor role [69]. Consequently, the potential for drug–drug interactions exist. The use of the drug is not recommended in those receiving simultaneous treatment with strong inhibitors of both CYP3A4 and P-gp (itraconazole, ketoconazole and others) [70]. Rifampicin, phenytoin, carbamazepine, phenobarbital and other strong CYP3A4 and P-gp inducers may also reduce plasma concentration of apixaban [66,71]. Therefore, the concomitant use of apixaban and these drugs should be done with caution.

Apixaban's pharmacodynamic properties show consistency across different ethnic groups, and are fairly maintained in those with mild-to-moderate hepatic impairment [72–74]. Renal excretion accounts for about 27% of apixaban's total clearance, and studies have shown that, compared with individuals with normal renal function, mild (CrCl 51–80 ml/min), moderate (CrCl 30–50 ml/min) and severe (CrCl 15–29 ml/min) renal dysfunction causes an increase in plasma concentration by 16, 29 and 44%, respectively [66].

Summary of phase III clinical trials of apixaban in thromboprophylaxis after elective major orthopedic surgery

Apixaban was approved in Europe in 2011 for the prevention of VTE after THA or TKA [75] and is now available in more than 50 countries. Nonetheless, apixaban is not yet FDA-approved for this indication in the USA. The drug has been submitted for approval by the FDA in 2013.

ADVANCE-1 trial—ADVANCE-1 was a double-blind, double-dummy study that assessed apixaban versus enoxaparin for thromboprophylaxis after TKA (Table 3) [76]. Patients were followed for 60 days after discontinuation of anticoagulation. The rate of DVT, non-fatal PE and death from any cause during treatment (primary efficacy outcome) was similar; 9% with apixaban (2.5 mg twice daily) and 8.9% with enoxaparin (30 mg twice daily), with both medications being started 12–24 h after surgery and continued for 10–14 days. The composite incidence of major bleeding and clinically relevant non-major bleeding was 2.9% with apixaban and 4.3% with enoxaparin ($p = 0.03$), and the adjudicated rate of major bleeding events was 0.7% with apixaban and 1.4% with enoxaparin ($p = 0.05$). The study also showed a low incidence of elevated aminotransferase enzyme levels and the criteria for hepatotoxicity were not met in any patient receiving apixaban. ADVANCE-1 concluded that

apixaban did not meet pre-specified statistical non-inferiority criteria compared with enoxaparin, but its use was associated with lower rates of clinically relevant bleeding and it had a similar adverse event profile [76]. Noteworthy is the lower rate of VTE among enoxaparin recipients in ADVANCE-1 (8.9%) compared with earlier studies (16%), meaning the trial ended up being under-powered to demonstrate the non-inferiority of apixaban [31].

ADVANCE-2 trial—In ADVANCE-2, another large randomized double-blind Phase III trial, the same dose of apixaban (2.5 mg twice daily) was assessed against 40 mg daily of enoxaparin (vs 30 mg twice daily in ADVANCE-1) in patients undergoing elective TKA (Table 3) [77]. Apixaban was started 12–24 h after surgery and continued for 10–14 days, while enoxaparin was started 12 h before surgery and continued for 10–14 days. The primary efficacy outcome was similar to that of ADVANCE-1. The statistical design of the study required non-inferiority of apixaban before evaluation testing for superiority. The primary efficacy outcome occurred in 15% of 976 patients who received apixaban versus 24% of 997 patients who received enoxaparin, corresponding to a significant RR, 0.62 (95% CI: 0.51–0.74; $p < 0.0001$) and a significant absolute RR of 9.3% (5.8–12.7%). There was no statistically significant difference in the rate of major or clinically relevant non-major bleeding between the two arms (4% in apixaban arm vs 5% in enoxaparin arm, $p = 0.09$) [77].

ADVANCE-3 trial—The ADVANCE-3 study compared apixaban with enoxaparin for thromboprophylaxis after THA [78]. In this double-blind, double-dummy study, 5407 patients undergoing THA were randomized to receive apixaban (2.5 mg twice daily) or enoxaparin (40 mg once daily). Prophylaxis was continued for 35 days after surgery, followed by bilateral venographic studies. The primary efficacy outcome was similar to the prior ADVANCE studies. Patients were also followed for an additional 60 days after the last intended dose of medication. Seventy-two percent of 1949 patients in the apixaban group and 71.0% of 1917 patients in the enoxaparin group were evaluable for the primary efficacy outcome, which occurred in 1.4% in the apixaban group versus 3.9% in the enoxaparin group (RR: 0.36; 95% CI: 0.22–0.54; $p 0.001$). The composite outcome of major and clinically relevant non-major bleeding occurred in 4.8% in the apixaban group and 5.0% in the enoxaparin group. The study concluded that apixaban was associated with lower rates of VTE, without increased bleeding, compared with enoxaparin [78].

Pooled & meta-analyses of NOACs

A pooled analysis of 10 randomized clinical trials of VTE prevention after THA and TKA including 32,144 patients showed that new NOACs were better than enoxaparin in terms of the composite end point of VTE incidence and all-cause mortality, and had a similar risk of major bleeding, with rivaroxaban having the highest risk of major bleeding and apixaban having the lowest [79]. A large meta-analysis was conducted on 16 randomized controlled trials of 38,747 patients who received rivaroxaban, dabigatran or apixaban compared with enoxaparin for thromboprophylaxis after TKA or THA. Compared with enoxaparin, the risk of symptomatic VTE was lower with rivaroxaban (RR: 0.48; 95% CI: 0.31–0.75) but similar with dabigatran (RR: 0.71; 95% CI: 0.23–2.12) and apixaban (RR: 0.82; 95% CI: 0.41–

1.64). Compared with enoxaparin, clinically significant bleeding was higher with rivaroxaban (RR: 1.25; 95% CI: 1.05–1.49) but similar with dabigatran (RR: 1.12; 95% CI: 0.94–1.35) and lower with apixaban (RR: 0.82; 95% CI: 0.69–0.98) [39].

Compliance with NOACs

Poor compliance, manifesting as overdosing, underdosing and/or erratic or incorrect dosing intervals, can be an issue with vitamin K antagonists (VKAs) and can result in diminished drug action or adverse effects [46,80,81]. Generally, compliance in clinical trials is higher than in real world settings. In the GLORY registry, the percentage of patients complying with VTE prophylaxis guidelines was 47–62% in THA and 61–69% in TKA [82]. Moreover, the registry showed that the proportion of patients consistent with the ACCP Guidelines was significantly greater for those receiving subcutaneous enoxaparin than those receiving oral warfarin (33% of THA and 48% of TKA patients on warfarin in the USA versus 63% of THA and 72% of TKA patients on LMWH in the USA) [82]. This difference reflects the preference among US providers for low-dose warfarin regimens (INR target 1.5–1.9) which is lower than the ACCP recommended target INR range of 2–3. Therefore, compliance with ACCP Guidelines is likely to be higher with NOACs than VKA since NOACs, similar to LMWH, come in standardized doses and do not require laboratory monitoring [46,83].

Safety of NOACs

In a retrospective observational cohort study on 5061 consecutive patients undergoing THA and TKA, rivaroxaban, was associated with a significantly lower rate of symptomatic VTE compared with enoxaparin (2.1 vs 4.1%), with a statistically lower rate of major bleeding (2.9 vs 7.0%), fewer surgical complications and a shorter length of hospitalization [84]. Although randomized clinical trials in orthopedic thromboprophylaxis found that dabigatran has comparable safety and apixaban has less bleeding than enoxaparin, there is no antidote available for any of the NOACs. Therefore, adverse effects could potentially last for hours until the drug is excreted. Until r-Antidote, the genetically engineered antidote for oral direct factor Xa inhibitors is available, management of bleeding associated with these agents will be more difficult than LMWH. Similarly, reversal of dabigatran will be difficult until its investigational antidote (Dabi-Fab) is available for clinical use. However, it is important to recognize that the incidence of major bleeding of sufficient severity to warrant reversal is likely to be extremely rare. Therefore, most providers will not see the absence of a specific antidote as a reason not to use these agents.

HIT is a prothrombotic condition that can complicate the use of heparin and, to a lesser extent, LMWH. HIT results from the production of autoantibodies against heparin-platelet factor 4 (PF4) complexes. HIT is treated by heparin discontinuation and the use of intravenous direct thrombin inhibitors such as bivalirudin and argatroban. Neither dabigatran nor rivaroxaban affected the interaction of PF4 or anti-PF4/heparin antibodies with platelets, suggesting both agents might represent alternative anticoagulation options in patients with a history of HIT, although neither is currently approved for this indication [85]. Similarly, apixaban is not expected to cause or exacerbate HIT.

Expert commentary: Which NOAC, when & how?

The choice of thromboprophylaxis for a patient depends upon the presence of co-morbid conditions, the patient's risk of VTE and bleeding, concomitant medications and patient preferences. The presence of severe renal dysfunction ($\text{CrCl} < 30 \text{ ml/min}$) would favor the use of a VKA plus mechanical compression therapy. Renally adjusted doses of enoxaparin plus mechanical compression therapy could be considered an option as well. We would avoid NOACs in these patients given that they were excluded from participation in the orthopedic thromboprophylaxis trials. In patients taking strong inhibitors or inducers of P-gp and/or CYP3A4, we would use caution with NOACs. For patients with an aversion to injections, NOACs would be the most effective choice. In patients with a high risk of bleeding (hemophilia), mechanical compression therapy alone would be preferred. Cost-effectiveness, especially comparative data between different agents, and insurance considerations are also likely important determinants of agent choice especially in light of recent changes in the healthcare system. These comments underscore the need to perform a thorough assessment of patients pre-operatively in order to optimize VTE prophylaxis.

Timing & duration of orthopedic thromboprophylaxis

The first dose of dabigatran should be administered 1–4 h after surgery once hemostasis has been achieved. If this has not been achieved, delaying the dose for more than 4 h or the next day has not been associated with a reduction in efficacy for the 220 mg daily dose [86]. Rivaroxaban 10 mg once daily should be started no sooner than 6–10 h post-operation once hemostasis has been achieved. Apixaban 2.5 mg twice daily is recommended to start 12–24 h after wound closure.

Using the linked California hospital discharge database, White *et al.* noted that the median time to diagnosis of VTE after TKA was 7 days compared with 17 days for THA. The incidence of VTE stabilized by 4 weeks after TKA and 10 weeks after THA [87]. Similar data were reported from a large Swedish observational cohort study; the median timing of VTE after TKA was 6 days (range 0–42 days) compared with 26 days (range 0–42 days) after THA [4]. These data support the 2012 ACCP Guideline suggestion to extend VTE prophylaxis for major orthopedic surgery from the minimum of 10–14 days up to 35 days. Given the time course of VTE after TKA and THA, longer prophylaxis is likely to be more beneficial for patients undergoing such orthopedic procedures. Consistent with the ACCP guidelines, we would recommend patients undergoing THA receive 35 days of VTE prophylaxis while patients undergoing TKA should receive at least 14 days. Longer duration prophylaxis (35 days) in TKA patients who have additional VTE risk factors such as failure to ambulate prior to discharge, age ≥ 75 years, known thrombophilia or a previous episode of VTE needs to be further investigated in future studies. We would prefer shorter course prophylaxis (14 days) in TKA patients deemed at higher risk for bleeding (thrombocytopenia, coagulopathy, liver or renal disease, etc.) Unfortunately, no validated risk stratification tool for VTE or bleeding exist for major orthopedic surgery, which limits the accuracy of risk factor assessment [88].

Current orthopedic VTE prophylaxis guideline recommendations

The 2012 ACCP orthopedic surgery VTE prophylaxis guidelines recommend low-dose unfractionated heparin (LDUH), LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban, adjusted dose VKA, aspirin (all Grade 1B) or intermittent pneumatic compression devices (IPCD) (Grade 1C) for a minimum of 10–14 days rather than no prophylaxis [88]. NOACs are only recommended for THA and TKA, not hip fracture surgery. Irrespective of the concomitant use of an IPCD or length of treatment, in patients undergoing THA or TKA, the use of LMWH is preferred over fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA or aspirin (all Grade 2C). The panelists recommended that IPCD be worn 18 h daily and that only portable battery-powered IPCD be used, as they are associated with higher compliance. Dual prophylaxis with an antithrombotic agent and an IPCD during hospital stay is suggested in patients undergoing major orthopedic surgery (Grade 2C). They suggest extending prophylaxis to 35 days rather than discontinuation after 10–14 days (Grade 2B). In patients at increased bleeding risk, they recommend IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C). In patients who refuse subcutaneous injections or IPCD, the use of apixaban or dabigatran (or alternatively rivaroxaban or a VKA) is recommended over other alternatives (all Grade 1B). They recommend against use of inferior vena cava (IVC) filters for primary prophylaxis over no thromboprophylaxis in patients with increased risk of bleeding (Grade 2C). In asymptomatic patients undergoing major orthopedic surgery, they also recommended against the routine use of venographic ultrasonography screening before hospital discharge (Grade 1B) [88].

The 2011 American Academy of Orthopedic Surgeons (AAOS) recommends against routine use of duplex ultrasound screening [102]. Providers should assess elective THA and TKA patients for additional VTE risk factors, and should also assess patients for the presence of inherited (i.e., hemophilia) or acquired (i.e., liver disease) bleeding disorders. They suggested that physicians discontinue anti-platelet agents (e.g., aspirin) before undergoing THA or TKA. Additionally, prescription of pharmacologic and/or mechanical prophylaxis for standard VTE risk patients undergoing elective THA or TKA was recommended. They did not favor one prophylaxis strategy due to the inconclusive nature of the available data in their opinion. Discussion of the appropriate duration of prophylaxis with all patients and the use of mechanical compressive devices for VTE prophylaxis for patients with bleeding disorders undergoing elective THA or TKA were recommended. The AAOS recommended that patients with a previous history of VTE should receive pharmacologic rather than mechanical VTE prophylaxis. They also recommended early mobilization for patients after elective THA and TKA and suggested that neuraxial anesthesia be utilized. The AAOS stated that current evidence was insufficient to recommend for or against the use of IVC filters for VTE prophylaxis [102]. We favor use of the ACCP guideline recommendations as we believe they give the provider more specific advice on VTE prevention in orthopedic surgery patients. Nevertheless, providers can find useful information for patient management in both guidelines.

Use of NOACs in patients with renal or hepatic impairment or coagulation disorders

Although randomized clinical trials for the NOACs included a large number of patients, patients were highly selected and important groups of patients with comorbid conditions,

such as patients with renal ($\text{CrCl} < 30 \text{ ml/min}$) and hepatic insufficiency, were excluded. This issue underscores the need for post-marketing studies in at-risk populations [46], especially since many orthopedic patients are elderly and have underlying renal and hepatic problems. Clinicians should calculate a Cockcroft-Gault CrCl for all patients and consider alternatives to NOACs for thromboprophylaxis in patients with severe renal dysfunction. The EMA-approved package insert recommends that dabigatran's dose be 150 mg once daily in those with moderate renal impairment ($\text{CrCl} 30\text{--}50 \text{ ml/min}$), and that it not be used in those 75 years of age or older or those with severe renal impairment ($\text{CrCl} < 30 \text{ ml/min}$) [103]. The US FDA- and EMA-approved package inserts' recommended dose for rivaroxaban for patients with moderate renal impairment ($\text{CrCl} 30\text{--}49 \text{ ml/min}$) remains 10 mg once daily [104,105]. The FDA-approved package insert for rivaroxaban advises that patients with moderate renal insufficiency ($\text{CrCl} 30\text{--}49 \text{ ml/min}$) be closely monitored for bleeding complications, and that rivaroxaban not be used when $\text{CrCl} < 30 \text{ ml/min}$ [101]. The EMA-approved package insert recommends caution when using rivaroxaban in patients with CrCl of 15–29 ml/min, and recommends not using the drug in patients with $\text{CrCl} < 15 \text{ ml/min}$ [105]. The EMA-approved package insert recommends no dose adjustment in patients on apixaban with mild ($\text{CrCl} 51\text{--}80 \text{ ml/min}$) or moderate ($\text{CrCl} 30\text{--}50 \text{ ml/min}$) renal impairment, and that it be used with caution in those with severe ($\text{CrCl} 15\text{--}29 \text{ ml/min}$) renal impairment [106]. It is contraindicated when $\text{CrCl} < 15 \text{ ml/min}$ [106].

Liver disease can influence drug disposition as well as coagulation factor synthesis and platelet production. Therefore, patients with clinically significant liver disease (Child–Pugh class B or C liver disease or hepatic transaminases > 2 -fold the upper limit of normal or total bilirubin > 1.5 -fold the upper limit of normal) were excluded from participation in the randomized clinical trials investigating the use of NOACs for orthopedic thromboprophylaxis. The FDA- and EMA-approved rivaroxaban package inserts recommend against the use of rivaroxaban in those with a Child–Pugh Class B or C hepatic impairment [104]. The EMA-approved package insert recommends against the use of dabigatran in those with elevated liver enzymes > 2 -times the upper limit of normal [103]. Apixaban's EMA-approved package insert recommends using caution with apixaban in patients with mild or moderate hepatic impairment (Child–Pugh A or B) and not using apixaban in those with more severe hepatic impairment [107].

Patients with a known coagulopathy (presumably elevated prothrombin time or aPTT) or a platelet count less than $100,000/\mu\text{l}$ were excluded from participation in the orthopedic thromboprophylaxis trials with apixaban. Similar exclusions are alluded to in the randomized trials of rivaroxaban for orthopedic thromboprophylaxis. In light of the potential impact of renal and hepatic disease or coagulation or platelet disorders on bleeding complications associated with NOACs, physicians should assess patients for the presence of these conditions by appropriate testing prior to surgery.

Drug–drug interactions & NOACs

Although the NOACs have fewer drug–drug interactions compared with warfarin, there is still a potential for drug–drug interactions when using these agents. Therefore, it is important for the clinicians to review each patient's medication list pre-operatively before considering

a NOAC for orthopedic thromboprophylaxis. The US FDA-approved package insert for dabigatran, mainly for non-valvular atrial fibrillation, cautions clinicians to avoid co-administration with P-gp inducers (lowers drug levels) [108]. Dronedarone, systemic ketoconazole or other P-gp inhibitors increase the drug's concentrations in the presence of moderate renal insufficiency (CrCl 30–50 ml/min), but no FDA recommendations exist for any dose adjustment in the setting of thromboprophylaxis in elective major orthopedic surgery [108]. The EMA recommends reducing the dose of dabigatran to 150 mg in patients taking amiodarone, verapamil or quinidine, as well as in patients more than 75 years of age with moderate renal impairment (CrCl 30–50 ml/min) [103]. They further advise caution during co-administration with mild to moderate P-gp inhibitors (like verapamil, amiodarone or quinidine) and recommend that the drug not be co-administered with strong P-gp inhibitors (like systemic ketoconazole, tacrolimus or dronedarone) or P-gp inducers (like rifampin or St. John's wort) [103]. The EMA and FDA package inserts recommend against concomitant use of rivaroxaban and the strong P-gp and CYP3A4 inhibitors ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan [104]. The EMA-approved apixaban package insert recommends against concomitant use of apixaban with ketoconazole and other strong P-gp and CYP3A4 inhibitors [107]. The package also recommends that rifampin and other strong P-gp and CYP3A4 inducers be co-administered with caution.

Neuraxial analgesia & NOACs

Therapeutic dose and high-dose prophylactic regimens of anticoagulants are associated with an increased risk of epidural hematoma in patients receiving neuraxial anesthesia [89]. In the RECORD program of orthopedic thromboprophylaxis, 4086 rivaroxaban patients and 4090 enoxaparin patients underwent neuraxial anesthesia. Indwelling epidural catheters were used in 913 rivaroxaban recipients and 897 enoxaparin treated patients. If pre-operative thromboprophylaxis was prescribed, placement of the epidural catheter was delayed until at least 12 h after the pre-operative injection. If an epidural catheter was placed for post-operative analgesia, it could not be withdrawn until at least 2 half-lives after the last dose of thromboprophylaxis (RECORD1–3) or 20 h after the last dose of prophylaxis (RECORD4). The next dose of prophylaxis could not be given until at least 4 h after catheter removal. One compressive epidural hematoma occurred in an enoxaparin-treated patient. No epidural hematomas due to rivaroxaban were noted [90]. The previously mentioned dabigatran trials (RE-MODEL, RENOVATE, RE-MOBILIZE) were re-visited in a pooled analysis performed on patients receiving general, neuraxial anesthesia or the combination of either with peripheral nerve block [91]. The analysis showed no significant difference in the effect of anesthesia type on the efficacy or safety of dabigatran compared with enoxaparin. There is currently no clinical experience on neuraxial anesthesia and the use of apixaban [107]. The European Society of Anesthesia Guidelines recommend that dabigatran, apixaban and rivaroxaban be held for 34, 26–30 and 22–26 h, respectively, before epidural catheter removal. The next dose should not be given until 2–6 h after catheter removal [92].

Five-year view

At the present time, rivaroxaban is the only NOAC approved for orthopedic thromboprophylaxis in the USA (Table 4). By contrast, apixaban, dabigatran and rivaroxaban have all been approved in Europe and in many other countries for orthopedic thromboprophylaxis. In the next 5 years, it is likely that the manufactures of apixaban and perhaps dabigatran will seek FDA approval for this indication in the USA. In addition, edoxaban, another oral direct factor Xa inhibitor that already has approval in Japan, could potentially enter the US market. We believe that acceptance of NOACs for orthopedic thromboprophylaxis will continue to increase as physicians and patients become more familiar with these agents. The availability of antidotes being actively investigated at present will undoubtedly accelerate acceptance of NOACs, as the irreversibility of these agents remains a concern. In addition, the absence of wide availability of laboratory tests to monitor the NOACs remains a limitation to broader use. For the near future, LMWH will remain an important alternative to NOACs for orthopedic thromboprophylaxis. Ultimately, we believe that NOACs will replace LMWH and warfarin for many of their indications given their oral route of administration, absence of dietary interactions, limited drug–drug interactions and absence of a requirement for laboratory monitoring. As clinical trials establish the efficacy and safety of novel NOACs in a wide spectrum of patients, it seems probable that there will be a gradual shift from conventional anticoagulants such as warfarin and LMWH to medications with easier routes of administration and more predictable anticoagulant effects requiring less frequent monitoring. It also seems likely that these NOACs gradually will be approved for the management of a wider variety of clinical conditions.

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Key issues

- The orthopedic patient population is at high risk for the development of venous thromboembolism (VTE) in the immediate and extended post-operative period.
- The need for anticoagulants with a more convenient route of administration, a better efficacy and safety profile and more predictable pharmacokinetics highlights the need for novel oral anticoagulants.
- The currently available novel oral anticoagulants include the direct thrombin inhibitor (dabigatran) and the FXa inhibitors (rivaroxaban and apixaban).
- Clinical trials comparing rivaroxaban, dabigatran and apixaban with the standard of care showed promising results in terms of efficacy for thromboprophylaxis and venous thromboembolism treatment among orthopedic patients, with a similar safety pattern.
- Anticoagulation reversal and the availability of laboratory monitoring tests remain issues of concern for clinicians, as reversal agents are still under investigation and specialized assays such as anti-Xa assays and the Hemoclot thrombin inhibition assay are required for assessment of drug levels.
- Although published clinical trials included large number of patients, these patients were highly selected and important groups of patients with comorbid conditions were excluded.
- While promising, these drugs need to be re-evaluated after being introduced to the market for any unexpected adverse effects.

Figure 1. A revised model of the coagulation cascade

In the initiation phase, TF activates FVII. TF-FVIIa complex then activates small amounts of factor IX and factor X, generating FIXa and FXa. FXa converts small amounts of prothrombin to thrombin, which in turn activates factors V and VIII. In the propagation phase, FIXa binds to platelet membranes and FVIIIa, forming the tenase complex, which catalyzes the production of more FXa. The prothrombinase complex (FXa + FVa) results in the production of massive amounts of thrombin, leading to the development of a blood clot. In the termination phase, thrombin generation is suppressed by APC and TFPI while thrombin, FXa and FIXa are inhibited by antithrombin III.

APC: Activated protein C; TAFI: Thrombin activatable fibrinolysis inhibitor; TF: Tissue factor; TFPI: Tissue factor pathway inhibitor.

Data taken from [93–95].

Table 1

Major Phase III clinical trials of rivaroxaban for thromboprophylaxis following elective total knee or total hip arthroplasty.

Trial	Study arms	Primary efficacy outcome definition	Primary efficacy outcome	Primary safety outcome definition	Primary safety outcome	Ref.
RECORD1	Rivaroxaban 10 mg once daily for 30–42 days Enoxaparin 40 mg once daily for 30–46 days	Composite of DVT (symptomatic or detected by bilateral venography), non-fatal PE or death from any cause at 36 days	18/1595 (1.1%) p-value vs enoxaparin <0.001 for superiority 58/1558 (3.7%)	Major bleeding (fatal bleeding; bleeding into a critical organ; or bleeding requiring re-operation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g per deciliter or that required transfusion of 2 or more units of whole blood or packed cells up to 2 days after last dose	6/2209 (0.3%) p-value vs enoxaparin = 0.18 2/2224 (0.1%)	[32]
RECORD2	Rivaroxaban 10 mg once daily for 31–39 days Enoxaparin 40 mg once daily for 10–14 days	Composite of DVT (symptomatic or detected by bilateral venography), non-fatal PE or death from any cause at 30–42 days	17/864 (2.0%) p-value vs enoxaparin <0.0001 for superiority 81/869 (9.3%)	Major bleeding up to 2 days from last intake (same definition as RECORD1 Trial)	81/1228 (6.6%) p-value vs enoxaparin = 0.25 68/1229 (5.5%)	[33]
RECORD3	Rivaroxaban 10 mg once daily for 13–17 days Enoxaparin 40 mg once daily for 13–17 days	Composite of DVT (symptomatic or detected by bilateral venography), non-fatal PE or death from any cause within 13–17 days	79/824 (9.6%) p-value vs enoxaparin = 0.01 for superiority 166/878 (18.9%)	Major bleeding up to 2 days from last intake (same definition as RECORD1 Trial)	7/1220 (0.6%) p-value vs enoxaparin = 0.77 6/1239 (0.5%)	[34]
RECORD4	Rivaroxaban 10 mg once daily for 11–15 days Enoxaparin 30 mg every 12 h for 11–15 days	Composite of DVT (symptomatic or detected by bilateral venography), non-fatal PE or death from any cause up to day 17 after surgery	67/965 (6.9%) p-value vs enoxaparin p = 0.0118 for superiority 97/959 (10.1%)	Major bleeding up to 2 days from last intake (same definition as RECORD1 Trial)	10/1526 (0.7%) p-value vs enoxaparin = 0.1096 4/1508 (0.3%)	[35]

DVT: Deep venous thrombosis; PE: Pulmonary embolism.

Table 2

Major Phase III clinical trials of dabigatran etexilate for thromboprophylaxis following elective total knee or total hip arthro-plasty.x

Trial	Study arms	Primary efficacy outcome definition	Primary efficacy outcome	Primary safety outcome definition	Primary safety outcome	Ref.
RE-NOVATE	Dabigatran etexilate 220 mg once daily for 28–35 days Dabigatran etexilate 150 mg once daily for 28–35 days Enoxaparin 40 mg once daily for 28–35 days	Composite of total venous thromboembolism (venographic or symptomatic) and death from all causes during treatment	53/880 (6.0%) p-value vs enoxaparin <0.001 for non-inferiority 75/874 (8.6%) p-value vs enoxaparin <0.001 for non-inferiority 60/897 (6.7%)	Major bleeding (fatal bleeding; bleeding into a critical organ; or bleeding requiring re-operation or extra-surgical-site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g/dl or that required transfusion of 2 or more units of whole blood or packed cells during treatment	23/1146 (2%) (p-value vs enoxaparin = 0.44) 15/1163 (1.3%) (p-value vs enoxaparin = 0.6) 18/1154 (1.6%)	[56]
RE-NOVATE II	Dabigatran etexilate 220 mg twice daily for 28–35 days Enoxaparin 40 mg once daily for 28–35 days	Composite of total venous thromboembolism (venographic or symptomatic) and death from all causes up to 3 days after last dose	61/792 (7.7%) p-value vs enoxaparin = 0.43 for non-inferiority 69/785 (8.8%)	Major bleeding events during treatment period as defined by criteria used in previously reported Phase III study	14/1010 (1.4%) (p-value vs enoxaparin = 0.4) 9/1003 (0.9%)	[57]
RE-MODEL	Dabigatran etexilate 220 mg once daily 6–10 days Dabigatran etexilate 150 mg once daily for 6–10 days Enoxaparin 40 mg once daily for 6–10 days	Composite of total venous thromboembolism (venographic or symptomatic) and death from all causes during treatment	183/503 (36.4%) p-value vs enoxaparin = 0.38 for non-inferiority 213/526 (40.5%) p-value vs enoxaparin = 0.82 for non-inferiority 193/512 (37.7%)	Occurrence of major bleeding, clinically relevant non-major bleeding, and minor bleeding events during treatment period as defined by criteria used in previously reported Phase III study	16/608 (1.5%) (p-value vs enoxaparin = 0.82) 9/625 (1.3%) (p-value vs enoxaparin = 1.0) 9/616 (1.3%)	[58]
RE- MOBILIZE	Dabigatran etexilate 220 mg once daily 12–15 days Dabigatran etexilate 150 mg once daily for 12–15 days Enoxaparin 40 mg once daily for 12–15 days	Composite of total venous thromboembolism (venographic or symptomatic) and death from all causes during treatment	188/604 (31.1%) p-value vs enoxaparin = 0.38 for non-inferiority 219/649 (33.7%) p-value versus enoxaparin = 0.82 for non-inferiority 163/643 (25.3%)	Occurrence of major bleeding during treatment period as defined by criteria used in previously reported Phase III study	5/857 (0.6%) (p-value vs enoxaparin = N/A*) 5/871 (0.6%) (p-value vs enoxaparin = N/A*) 12/868 (1.4%)	[59]

* p-value not stated in the trial.

Table 3

Major Phase III clinical trials of apixaban for thromboprophylaxis following elective total knee or total hip arthroplasty.

Trial	Study arms	Primary efficacy outcome definition	Primary efficacy outcome	Primary safety outcome definition	Primary safety outcome	Ref.
ADVANCE-1	Apixaban 2.5 mg twice daily for 10–14 days Enoxaparin 30 mg twice daily for 10–14 days	Composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE or death from any cause during treatment period	104/1157 (9%) p-value vs enoxaparin = 0.06 for non-inferiority 100/1130 (8.8%)	Major bleeding or clinically relevant non-major bleeding during the treatment period or within 2 days after the last dose of study	46/1596 (2.9%) (p-value vs enoxaparin = 0.03) 68/1588 (4.3%)	[76]
ADVANCE-2	Apixaban 2.5 mg twice daily for 10–14 days Enoxaparin 40 mg once daily for 10–14 days	Composite of adjudicated asymptomatic or symptomatic DVT, non-fatal PE and all-cause deaths during the intended treatment period or within 2 days of last dose of study drug, whichever came first	147/976 (15%) p-value vs enoxaparin <0.0001 for superiority	Adjudicated major or clinically relevant non-major bleeding events during treatment	53/1501 (4%) (p-value vs enoxaparin = 0.09)	[77]
			243/997 (24%)	72/1508 (5%)		
ADVANCE-3	Apixaban 2.5 mg twice daily for 32–38 days Enoxaparin 40 mg once daily for 32–38 days	Adjudicated asymptomatic or symptomatic DVT, non-fatal PE or death from any cause during the intended treatment period	27/1949 (1.4%) p-value vs enoxaparin <0.001 for non-inferiority and superiority 74/1917 (3.9%)	Adjudicated major or clinically relevant non-major bleeding events during treatment period	129/2673 (4.8%) (p-value vs enoxaparin = 0.72) 134/2659 (5%)	[78]

DVT: Deep venous thrombosis; PE: Pulmonary embolism.

Table 4

Comparison between the currently used agents and the novel oral anticoagulants in thromboprophylaxis following elective total knee or total hip arthroplasty.

Anticoagulant	Dose for thromboprophylaxis	FDA approval status for thromboprophylaxis in THA and TKA	Half-life	Time of initiation relative to surgery	Approved duration of prophylaxis
Rivaroxaban	10 mg by mouth once daily	Yes	5–9 h	6–10 h after surgery	35 days for hip replacement 12 days for knee replacement
Dabigatran etexilate	150 mg by mouth once daily or 220 mg by mouth once daily (Half dose- 75 mg or 110 mg given for first dose)	No	12–17 h	1–4 h after surgery	28–35 days for hip replacement 10 days for knee replacement
Apixaban	2.5 mg by mouth twice daily	No	12 h	12–24 h after surgery	28–35 days for hip replacement 10–14 days for knee replacement
Enoxaparin	40 mg subcutaneously once daily or 30 mg subcutaneously twice daily	Yes	7 h	12–24 h after surgery (for the 30 mg twice-daily dose) 40 mg once-daily dose started at the night prior to orthopedic surgery in the NOAC trials	35 days for hip replacement 10–14 days for knee replacement
Fondaparinux	2.5 mg subcutaneously once daily	Yes	17–21 h	6–8 h after surgery	35 days for hip replacement 10–14 days for knee replacement
Dalteparin	<50 kg: 2500 IU subcutaneously once daily 50–100 kg: 5000 IU subcutaneously once daily 100–150 kg: 5000 IU subcutaneously twice daily >150 kg: 7500 IU twice daily	Yes	3–5 h	May start 10–14 h prior to surgery and continue after surgery May alternatively start 4–8 h after surgery	28–35 days for hip replacement 10–14 days for knee replacement
Tinzaparin	75 IU/kg or 4500 IU subcutaneously once daily	Yes	3.9 h	6–12 h after surgery	28–35 days for hip replacement 10–14 days for knee replacement
Warfarin	Dosing to prolong INR (international normalized ratio) to 2–3	Yes	40 h	12 h before surgery	35 days for hip replacement 12 days for knee replacement

IU: International Unit; NOAC: Novel oral anticoagulant; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.