Apixaban for the Prevention of Thromboembolism in Adults after Elective Hip or Knee Replacement Surgery, and in Symptomatic Venous Thromboembolism

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Abstract: The anticoagulant effect of apixaban is due to direct inhibition of FXa in the coagulation cascade. The main advantages apixaban has over the current anti-coagulant drugs is that it is active after oral administration, and its coagulation effect does not require monitoring. Apixaban has been compared to enoxaparin in the prevention of venous thromboembolism associated with knee and hip replacement, where it is as efficacious as enoxaparin, but causes less bleeding. However, apixaban is not the only FXa inhibitor that could replace enoxaparin for this indication, as the FXa inhibitor rivaroxaban is as efficacious and safe as enoxaparin in preventing thromboembolism associated with these surgical procedures. Until the results of the AMPLIFY Phase III trial are known, it is too early to consider apixaban as an alternative to enoxaparin in symptomatic thromboembolism. Apixaban should not be used to prevent thromboembolism in medical immobilised subjects or acute coronary syndromes, as it causes excess bleeding in these conditions without benefit.

Keywords: apixaban, enoxaparin, hip replacement, knee replacement, rivaroxaban, venous thromboembolism

Introduction

Chronic hip or knee pain, and the need for surgical replacement, is highly prevalent among older people. For instance, the English Longitudinal Study of Ageing has shown that 20% of people aged 60 years and over, either need or have had hip or knee replacement.[1] Without anticoagulants, as many as 7% of subjects, undergoing surgery for fractured hips, would die from pulmonary embolism resulting from venous thromboembolism.[2] Furthermore, without thromboprophylaxis, 40%–60% of subjects undergoing major orthopaedic surgery, and 10%–20% of subjects with acute medical conditions leading to immobilisation will develop deep vein thrombosis.[3]

The currently used anticoagulant agents are un fractionated heparin, low-molecular weight heparins, the indirect inhibitor of Factor Xa fondaparinux, and warfarin. Although effective in some cases, these treatments are difficult to use because of the need for injections initially with heparin/heparins and fondaparinux, and for frequent laboratory monitoring and dose adjustments with the Vitamin K antagonists, such as warfarin.[4,5] There are also frequent drug and dietary interactions, and variability in the response to the Vitamin K antagonists.[2] Even with prophylaxis, subclinical deep-vein thrombosis develops in about 15%–20% of subjects soon after hip replacement, and symptomatic venous thromboembolism develops in 2%–4% of subjects in the first three months after surgery.[3]

Factor Xa (FXa) is the penultimate enzyme in the coagulation cascade, and is also at the intersection of the intrinsic and extrinsic pathway. FXa combines with factor Va and calcium to form the prothrombinase complex that converts prothrombin to thrombin. Thrombin generation is an important component of the coronary arterial thrombosis that follows atheromatous plaque disruption. In response to vascular injury, thrombin stimulates platelets, amplifies further thrombin formation, converts soluble fibrinogen to insoluble fibrin (the clot), stabilizes the fibrin meshwork, and initiates the cytokine-mediated inflammatory process.

Attention on inhibiting FXa as an approach to anti-coagulation arose from the finding that low-molecular-weight heparins (LMWH), which inhibit FXa to a greater extent than unfractionated heparin, were superior to the unfractionated heparin in the treatment of venous and arterial thrombosis.[6] By inhibiting a late stage in coagulation, it was postulated that the effects of inhibitors of FXa would have less variability, and require less monitoring than the presently used anticoagulants. Thus, direct inhibition of FXa seems a rational approach to the treatment of thromboembolism.

Using razaxaban as their lead compound, Bristol-Myers Squib developed apixaban, as a direct FXa inhibitor. The clinical trials with apixaban have been in association with Pfizer. In this review, after discussing the preclinical pharmacology of apixaban, the clinical trials of apixaban in elective hip or knee replacement, in symptomatic venous thromboembolism, and in prevention of venous thromboembolism in medical subjects are discussed, prior to consideration of the place in therapy apixaban has, in these conditions.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

As a direct inhibitor of FXa, razaxaban was the predecessor to apixaban. Razaxaban was a highly potent, selective, and orally bioavailable FXa inhibitor developed by Bristol-Myers Squibb for the prevention and treatment of venous and arterial thrombosis.[7] In clinical trial for prevention of deep vein thrombosis in knee replacement surgery, razaxaban decreased the incidence of thrombosis, but also increased the bleeding. The rate of thromboembolism was 15.9% with enoxaparin and was lowered to 8.6, 6.0, 3.6, and 1.4% with razaxaban at 25, 50, 75 and 100 mg/bid, respectively. The major bleeding rate was 0.0% with enoxaparin, and 0.7, 4.1, 3.5 and 5.8% with razaxaban at 25, 50, 75 and 100 mg/bid, respectively,[7] and this necessitated stopping the study with the 3 higher doses of razaxaban.

Apixaban (BMS-562247) is 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, and is a competitive inhibitor of FXa.[8] Apixaban is more selective for human FXa ($K_i = 0.08$ nM) over thrombin ($K_i = 3100$ nM)[7] than razaxaban was (FXa, 0.19 nM, thrombin, 600 nM;[7]). Apixiban has a similar potency against free FXa and fibrin clot-bound FXa.[9] In human plasma, apixaban inhibited prothrombin time (PT, a measure of the extrinsic coagulation pathway) and human partial activated thromboplastin time (aPTT, a measure of both the intrinsic and common coagulation pathways) with

EC_{2x} (effective concentration that inhibited 2-fold) values of 3.6 and 7.4, respectively,[8] but had no effect on platelet aggregation.[9]

In a model of arterial thrombosis (carotid artery thrombosis in the rabbit), the infusion of apixaban ($\geq$0.03 mg/kg/h) increased the patency of the artery measured as carotid blood flow.[10] In the rabbit cuticle bleeding time model, apixaban 3 mg/kg/h increased bleeding time by 1.2-fold, whereas warfarin 3 mg/kg/day po increased bleeding 6.2-fold.[10]

As apixaban is likely to be used in combination with antiplatelet agents in humans, preclinical combination studies with aspirin and clopidogrel have been undertaken. In the rabbit model of arterial thrombosis, both aspirin 1 mg/kg/h iv and clopidogrel 3 mg/kg/day po, alone or in combination, partially prevented the reduction in carotid blood flow and reduced thrombus weight. In the presence of aspirin, apixaban (0.3 mg/kg/h iv) further prevented the reduction in carotid blood flow and thrombus weight. In the presence of aspirin and clopidogrel, apixaban (0.04 mg/kg/h iv) abolished the reduction in carotid blood flow and thrombus formation. Aspirin and aspirin with apixaban 0.04 or 0.3 mg/kg/h iv did not have any effect on rabbit cuticle bleeding time. In contrast, clopidogrel alone prolonged bleeding time, but this prolongation was not altered by the addition of apixaban 0.04 or 0.3 mg/kg/h iv. Only at 2.1 mg/kg/h iv, did apixaban prolong the bleeding time with aspirin and clopidogrel.[11]

In addition to FXa inhibitors, direct thrombin inhibitors such as dabigatran are being developed as anticoagulants. In a model of venous thrombosis, threads in the venae cavae of rabbits to cause partial occlusion in the anaesthetised rabbit, apixaban was more potent than dabigatran at inhibiting thrombus formation (EC_{50} of 65 nM versus 194 nM). At doses for 80% reduction in thrombus formation, apixaban and dabigatran prolonged bleeding time by 1.13 and 4.4 fold. This shows that apixaban prevents thrombus formation, without having a major effect on bleeding, whereas doses of dabigatran that are antithrombotic may also cause bleeding, at least in the rabbit.[12]

The metabolism of apixaban is different in humans than in mice, rats, rabbits, and dogs, and consequently the results in humans are mainly discussed.[13] In humans, apixaban is rapidly absorbed, and the maximal plasma level was achieved in about an hour, and an average $T_{1/2}$ of 12.7 hours.[14] Apixaban is metabolised by O-demethylation, hydroxylation, and sulfation of the hydroxylate.[14] To my knowledge, the metabolites have not been tested for activity. O-Demethyl apixaban sulphate represented about 25% of the parent curve under the time curve in human plasma.[13] The sulfotransferases (SULTs) capable of forming O-demethyl apixaban sulphate were SULT1A1 and SULT1A2, and as inhibition of SULT1A1 reduced the formation of O-methyl apixaban sulphate by 99%, it is likely that it is this SULT that is involved in the formation of the sulphate.[15] About half of the apixaban is eliminated in the faeces, and about a quarter in the urine, with only minor biliary elimination.[14] About half of the apixaban was eliminated as apixaban, which will reduce the number of possible drug interactions with apixaban.[14]

In vitro studies with human liver microsomes, showed that apixaban did not inhibit CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) or induce CYP enzymes (CYP1A2, 2B6, 3A4/5). The metabolism of apixaban by the microsomes was slow. This suggests that the potential for drug interactions with apixaban is low.[16]

Clinical Studies in Total Knee Replacement

The first medical condition that apixaban was tested in was in subjects having a total knee replacement, and apixaban was used to prevent thromboembolism (Table 1).

The Phase II clinical trial (APROPOS, Apixaban PROphylaxis in Patients undergoing tOtal knee replacement Surgery) compared six doses of apixaban with enoxaparin and warfarin in 1238 subjects, scheduled to have a total knee replacement. In APROPOS, apixaban (2.5 mg twice daily, or 5 mg once daily) were shown to be as least as good as, if not better than, enoxaparin or warfarin at preventing venous thromboembolism. The subjects enrolled in APROPOS had a mean age of ~63 years, and most were having a total knee replacement for arthritis (~70%), and the others had a degenerative joint. The primary efficacy outcome was a composite of asymptomatic and symptomatic deep vein thrombosis or non-fatal symptomatic pulmonary embolism or death (from any cause) and this was about 10% or less with the doses of apixaban, which was less than

Table 1. Efficacy and safety of apixaban in total knee and hip replacement and in deep vein thrombosis.

Trial, subjects, and design	Safety	Efficacy	Reference
Phase II APROPOS: Six doses of apixaban were compared with enoxaparin (30 mg bid sc) and warfarin in 1238 subjects undergoing total knee replacement	No major bleeds with apixaban 2.5 mg bid or with enoxaparin and warfarin. Major bleeding was observed with higher doses of apixaban	Less of the composite of asymptomatic and symptomatic deep vein thrombosis, or non-fatal symptomatic pulmonary embolism or death with apixaban than with enoxaparin and warfarin	17
Phase III ADVANCE-1: Apixaban 2.5 mg bid compared with enoxaparin (30 mg sc) in ~3000 subjects undergoing total knee replacement	Major and clinically relevant bleeding was less with apixaban than with enoxaparin	Non-inferiority of apixaban versus enoxaparin in the composite of asymptomatic and symptomatic deep vein thrombosis, or non-fatal symptomatic pulmonary embolism or death	19
Phase III ADVANCE-2: Apixaban 2.5 mg bid compared with enoxaparin (40 mg sc) in 1973 subjects undergoing total knee replacement	Major, clinically relevant, nonmajor bleeding and minor bleeding were similar with apixaban and enoxaparin	Less of the composite of asymptomatic and symptomatic deep vein thrombosis, or non-fatal symptomatic pulmonary embolism or death with apixaban than with enoxaparin	20
Phase III ADVANCE-3: Apixaban 2.5 mg bid compared with enoxaparin (40 mg sc) in 5407 subjects undergoing total hip replacement	Bleeding occurred in similar percentage in the apixaban and enoxaparin groups	Less of the composite of asymptomatic and symptomatic deep vein thrombosis, or non-fatal symptomatic pulmonary embolism or death within 2 days of last treatment with apixaban than with enoxaparin	22
The Botticelli DVT dose-ranging study: Apixaban 5, 10 or 20 mg bid was compared to a LMWH followed by a Vitamin K antagonist in 520 subjects with symptomatic deep vein thrombosis or extensive calf vein thrombosis	Similar composite of major and clinically relevant non-major bleeding in the apixaban and LMWH/ Vitamin K antagonist groups	Composite of symptomatic recurrent venous thromboembolism and asymptomatic deterioration in the thrombotic burden occurred similarly with the three doses of apixaban and the LMWH/ Vitamin K antagonist	23
Phase III ADOPT: Apixaban 2.5 mg bid was compared to enoxaparin 40 mg sc in 4495 subjects hospitalised for an acute medical condition, which limited their mobility	More major bleeding with apixaban than with enoxaparin	The 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis or asymptomatic proximal-leg deep-vein thrombosis occurred similarly in the apixaban and enoxaparin groups	27

the 15%–25% with enoxaparin or warfarin. The reduction with apixaban mainly represented reduced asymptomatic deep vein thrombosis, compared to that with enoxaparin or warfarin.[17]

In APROPOS, there were no major bleeds with apixaban at 2.5 mg twice daily orally or with enoxaparin or warfarin. But, in total knee replacement, major bleeds were observed in 2.6% (4 of 151 subjects), 2.6%, 0.6%, 2.6%, and 3.3% of subjects with apixaban at 5 mg (once daily), 5 mg (twice daily), 10 mg (once daily), 10 mg (twice daily) and 20 mg (once daily), respectively. The minor

bleeding with apixaban was similar to that observed with enoxaparin or warfarin. One subject taking apixaban at 2.5 mg twice daily died from pulmonary embolism, and two subjects died after the treatment with apixaban was complete. None of the subjects taking enoxaparin or warfarin died.[17]

On the basis of APROPOS, some modelling was done to determine the best dose to use in a Phase III study of apixaban to prevent venous thromboembolism. This modelling was used to get the therapeutic utility index, which was a measure of the efficacy/safety balance, and this was best at 86.2% for apixaban with the dose of 2.5 mg twice daily, which gave a better result than apixaban at 5 mg/twice daily (82%). The lower dose of apixaban also gave a better therapeutic utility index than enoxaparin 30 mg twice daily (82.5%) and warfarin (71.8%). Importantly, the modelling showed that with the lower dose of apixaban (2.5 mg twice daily), although the levels of apixaban would increase, there would be no need for dose adjustment in moderate renal impairment, which is a major advantage over the Vitamin K antagonists.[18]

The Phase II APROPOS clinical trial was followed by the Phase III ADVANCE-1 (Apixaban Dosed orAlly Vs. ANtiCoagulation with enoxaparin) trial, which compared apixaban 2.5 mg twice daily with enoxaparin 30 mg subcutaneously every 12 hours, started 12–24 hours after total knee replacement. In ADVANCE-1, apixaban was shown to have similar efficacy to enoxaparin, but to cause less bleeding. About 3000 subjects were enrolled in ADVANCE-1, and they were predominantly female (~61%) and White (~95%), and <4% had a history of venous thromboembolism. Most were undergoing a knee replacement because of osteoarthritis (~81%) followed by degenerative joint disease (~22%), and a few with rheumatoid arthritis (~2%). Subjects were followed for 60 days after anticoagulation therapy was stopped. The primary efficacy outcomes was the composite of asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism or death from any cause, and this occurred in 104 of 1157 subjects in the apixaban group (9%) compared to 100 of 1130 (8.8%) in the enoxaparin group, which shows that apixaban is not inferior to enoxaparin (confidence interval, CI, −2.2 to 2.4, $P < 0.001$).[19]

In ADVANCE-1, the primary safety outcome was bleeding, including major bleeding, clinically relevant nonmajor bleeding, and minor bleeding, and this occurred in 5.3% of subjects treated with apixaban and 6.8% of subjects treated with enoxaparin. Major bleeding occurred in less (0.7%) subjects treated with apixaban than treated with enoxaparin (1.4%, CI, −1.49 to −0.14%; $P = 0.053$), as was the composite of major bleeding and clinically relevant nonmajor bleeding (2.9% vs. 4.3%, CI, −2.75 to −0.17%; $P = 0.03$).[19]

In a second Phase III clinical trial (ADVANCE-2), apixaban 2.5 mg twice daily was compared with a slightly higher dose of enoxaparin, 40 mg, which is the commonly used dose, and in ADVANCE-2, enoxaparin was started 12 hours before the operation to replace the knee. ADVANCE-2 showed greater efficacy with apixaban than enoxaparin, but similar bleeding. The population in ADVANCE-2 was slightly different than in ADVANCE-1, having a higher percentage of females (~72%), but less White (~80%) and more Asian (~16%) subjects. However, the indications for surgery were similar in ADVANCE-1 and ADVANCE-2. The primary efficacy endpoint was also similar in ADVANCE-2 to ADVANCE-1, and, after 60 days, had occurred in less subjects in the apixaban group (147 of 976, 15.1%) than the enoxaparin group (243 of 997, 24.4%, CI, 0.51 to 0.74, $P < 0.0001$), and this reduction was predominantly due to a decrease in all deep vein thrombosis (14.6% vs. 24.4%). Bleeding occurred in similar numbers of subjects in the apixaban group (6.9%) and enoxaparin group (8.4%), and there were also similar percentages in the component groups that made up bleeding ie, major bleeding, clinically relevant nonmajor bleeding, and minor bleeding.[20]

A meta-analysis of the Phase II APROPOS[18] and the two Phase III ADVANCE trials[19,20] of apixaban versus enoxaparin in total knee replacement showed that there was less proximal deep vein thrombosis with apixaban (0.6%) than enoxaparin (1.2%, CI, 0.27 to 0.82, $P = 0.007$), and similar very low levels of pulmonary embolism and death with these drugs. Major bleeding was also less in the apixaban (0.6%) than the enoxaparin group (1.2%, CI, 0.32 to 0.96, $P = 0.034$), but was similar between the groups for clinically relevant non-major bleeding.[21]

Clinical Studies in Total Hip Replacement

As a result of apixaban being shown to have a better efficacy, with a similar or lower risk of bleeding in knee replacement to enoxaparin, apixaban was also tested, as an anticoagulant, in total hip replacement (Table 1). Apixaban was shown to be more effective than enoxaparin in preventing thromboembolism after hip surgery. Thus, the ADVANCE-3 trial compared apixaban 2.5 mg twice daily with enoxaparin 40 mg subcutaneously one daily for thromboprophylaxis after hip replacement. Enoxaparin was initiated 12 hours before surgery and apixaban was started 12–24 hours after the surgery, and continued for 32–38 days. The 5407subjects enrolled were slightly more women (~53%) than men, were on average about 60 years old, and were predominantly White (92%). Most of the enrolled had no history of venous thromboembolism (~98%), but some had had hip replacement previously (~23%), or surgery to repair a hip or knee fracture (~7%) or knee replacement (~4%). Most were having a hip replacement because of osteoarthritis (~57%) or degenerative joint disease (~24%).[22]

The primary efficacy outcome of ADVANCE-3 was the composite of asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause, within two days of the last treatment. This efficacy outcome occurred in 27 of 1949 subjects in the apixaban group (1.4%), which was less than the 74 of the 1917subjects in the enoxaparin group (3.9%, CI, 0.22 to 0.54, $P < 0.001$). Major venous thromboembolism occurred less with apixaban (0.5%) than with enoxaparin (1.1%, CI, 0.15 to 0.80, $P < 0.01$). The primary safety outcome was bleeding during the same period, and this occurred in a similar percentage of apixaban-treated subjects (11.7%) and enoxaparin-treated subjects (12.6%). The components of the bleeding endpoint were also similar for major bleeding events (apixaban, 0.8%; enoxaparin, 0.7%), clinically relevant nonmajor bleeding (4.1% vs. 4.5%) and minor bleeding (6.9% vs. 7.5%).[22]

Clinical Trials in Symptomatic Deep Vein Thrombosis

The standard treatment of deep vein thrombosis has been 5–10 days of body weight adjusted subcutaneous low molecular weight heparins (LMWH) or fondaparinux, then oral anti-coagulants, notably the vitamin K antagonist warfarin.[4,5] Although effective, this treatment is difficult because of the need for injections initially, and for frequent laboratory monitoring and dose adjustments with the vitamin K antagonists.[4,5]

Oral apixaban has been compared to LMWH and vitamin K antagonist in symptomatic deep vein thrombosis in the Botticelli DVT dose-ranging study, and shown to have a similar efficacy and safety in preventing further thromboembolism (Table 1). The study enrolled 520 consecutive subjects with symptomatic deep vein thrombosis or extensive calf vein thrombosis, and of these about 25% had had surgery trauma in previous three months, and ~20% had a history on venous thromboembolism. The subjects were randomised to apixaban 5 mg twice-daily, 10 mg twice daily, or 20 mg twice daily, or to LMWH followed by a vitamin K antagonist. The most common LMWH used was enoxaparin in 76% of subjects. The vitamin K antagonists (warfarin, acenocoumarol or phenprocoumon) were started 48 hours after randomisation and the doses were adjusted to maintain the International Normalised Ratio within the therapeutic range. The primary efficacy outcome was the composite of symptomatic recurrent venous thromboembolism and asymptomatic deterioration in the thrombotic burden. This primary efficacy outcome occurred similarly with the three doses of apixaban groups, which were combined to give an occurrence of 17 in the 358 apixaban-treated subjects (4.7%), which was a similar percentage to the five of the 118 LMWH/Vitamin K antagonist group (4.2%, not significantly different). There was one death in the 20 mg once-daily apixaban group, which may have been a fatal pulmonary embolism, but an autopsy was not undertaken to confirm this.[23]

In the Botticelli study the principal safety outcome was the composite of major and clinically relevant non-major bleeding and this occurred in 28 (7.3%) of the apixaban-treated subjects, and in 10 (7.9%, not significantly different) of the LMWH/Vitamin K antagonist group.[23] A study of the biomarkers of the coagulation activity in the Botticelli study showed that the levels of plasma D-dimer, prothrombin fragment 1 + 2, and thrombin-antithrombin complex levels were elevated at baseline, and were normalised in most subjects in both treatment groups, which is consistent with low rate of recurrent venous thromboembolism.[24]

The Phase III NCT00643201 (AMPLIFY, Apixaban after the initial Management of PuLmonary embolIsm and deep vein thrombosis with First-line therapY) trial that is underway is comparing apixaban to enoxaparin followed by warfarin, to prevent further venous thromboembolism. AMPLIFY is using an apixaban dose of 10 mg twice daily, for 7 days, followed by 5 mg twice daily for 6 months. This trial will continue recruiting men and women with deep vein thrombosis or pulmonary embolism until there are about 5000 enrolments, and the primary outcome is a composite of venous thromboembolism recurrence or death.[25] There is also an extension (AMPLIFY-EXT) trial of apixaban in deep vein thrombosis and pulmonary embolism, and the main differences are that NCT00633893 is a placebo-controlled trial comparing the lower doses of apixaban 2.5 mg or 5 mg twice daily, over a longer period ie, 12 months.[26] It is interesting that between them the ongoing trials will investigate a range of doses of apixaban, including the dose (2.5 mg twice daily) that gave the best result in the modelling.[18]

Clinical Trials to Prevent Symptomatic Venous Thrombosis

Venous thromboembolism is common and potentially fatal complication in acutely ill subjects, who are immobilised. A Phase III study of apixaban for the prevention of thrombosis-related events in patients with acute medical illness (ADOPT, Apixaban Dosing to Optimize Protection from Thrombosis, NCT00457002) has recently been reported (Table 1). In ADOPT, apixaban did not have any benefit compared to enoxaparin, but did increase major bleeding, compared to enoxaparin. Subjects with existing venous thromboembolism or active bleeding or at a high risk of bleeding were excluded from ADOPT. In ADOPT, apixaban 2.5 mg twice daily was compared to enoxaparin 40 mg subcutaneous in 4495 subjects hospitalized for acute medical condition, who were moderately or severely restricted in their mobility. These acute medical conditions included congestive heart failure, acute respiratory failure, infection, acute rheumatic disorder or inflammatory bowel disease. Except for subjects with congestive heart failure or respiratory failure, subjects also had to have one of the following risk factors; ≥75 years old, previous venous thromboembolism for which they received anticoagulant treatment, a body mass index of ≥30, or oestrogenic hormone treatment.[27]

The primary outcome measure in ADOPT was the 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis or asymptomatic proximal-leg deep-vein thrombosis, and this occurred in 2.71% of the apixaban group and 3.06% in the enoxaparin group. Major bleeding occurred in 0.47% of the subjects in the apixaban group, which was significantly more than the 0.19% in the enoxaparin group (CI, 1.02 to 7.24; $P = 0.04$).[27]

Subjects with cancer receiving treatment are at an increased risk of venous embolism, but at present, the available anticoagulants are not considered suitable to prevent this. A Phase II study of apixaban for the prevention of thromboembolism in subjects with advanced (metastatic) cancer has been completed (NCT00320255, ADVOCATE, ADVOCATE apixaban treatment to lower thromboembolism in cancer). This study enrolled subjects with advanced or metastatic cancer, who had had chemotherapy of ≥90 days, and were within 6 weeks of start of chemotherapy. The dose of apixaban being used is 5 mg, once daily.[28] Preliminary results from this study have shown there were three cases of venous thromboembolism and one major bleed in the placebo group of 30 subjects. There was no venous thromboembolism with apixaban, but there was one case of clinically relevant non-major bleeding in 32 subjects treated with apixaban 5 mg daily, and in 30 subjects treated with apixaban 10 mg, which suggests that the benefit may be greater than the bleeding with these doses.[29] However, apixaban at 20 mg daily caused two major bleeds and two clinically relevant non-major bleeds,[29] which suggests that this dose has too many detrimental effects to be considered for this indication.

Place in Therapy
Thromboembolism associated with knee and hip replacement

The standard treatment to prevent thromboembolism associated with knee and hip replacement was enoxaparin, and thus it was obvious that comparator trials with apixaban should be against enoxaparin. In knee (section 3) and hip replacement (section 4), apixaban has been shown to be as least as efficacious as enoxaparin, but to cause less bleeding. Also, apixaban

is easier to use than enoxaparin. This may suggest that apixaban should replace enoxaparin to prevent thromboembolism associated with knee and hip replacement. However, there is a complication; two other new anticoagulants have also recently been developed and shown to be better than enoxaparin in preventing thromboembolism associated with these surgical procedures. These anti-coagulants are another direct FXa inhibitor, rivaroxaban, and the direct thrombin inhibitor dabigatran.

Rivaroxaban is another direct FXa inhibitor that is active after oral administration.[30] Like apixaban, rivaroxaban has also been compared to enoxaparin in knee and hip replacement. A pooled analysis of four Phase III studies of 12,729 subjects having knee or hip replacement has shown that the primary efficacy endpoint of symptomatic venous thromboembolism or all-cause mortality occurred in less subjects with rivaroxaban than with enoxaparin (0.5% vs. 1%).[31] Major bleeding, major plus non-major clinically relevant bleeding, and any bleeding occurred in similar numbers of subjects in the rivaroxaban and enoxaparin group.[31] This suggests that rivaroxaban may also be preferred to enoxaparin after surgical procedures, as it a little bit more efficacious with good safety, and is easier to use.

This leads to a difficult question to answer at present—should apixaban or rivaroxaban be used instead of enoxaparin in knee and hip replacement? To answer this, a direct comparator trial of apixaban and rivaroxaban, in knee and/or hip replacement should be undertaken, but to my knowledge, this is not presently being done.

Dabigatran has been shown to be as effective and have a similar safety profile to enoxaparin in preventing venous thromboembolism after total knee replacement. In this study, 2076 subjects undergoing total knee replacement were randomised to dabigatran or enoxaparin for 30 days. The primary efficacy outcome was a total of venous thromboembolism and death, and this occurred in similar percentages of subjects treated with dabigatran and enoxaparin (36.4% vs. 37.7%). The primary safety outcome was the incidence of bleeding events, and that was also similar in the dabigatran and enoxaparin groups.[32] Similarly, dabigatran has been shown to have a similar efficacy and safety profile to enoxaparin in subjects at risk of venous thromboembolism

after hip replacement.[33] Like apixaban, dabigatran is easier to use than enoxaparin as it is active after oral administration and coagulation monitoring is not required, and it was on this basis that it was suggested that dabigatran is an attractive alternative to enoxaparin in total hip replacement.[33]

Recently, the FDA has started to investigate some serious bleeding events that have been reported with dabigatran.[34] Until this matter is resolved, dabigatran should not be considered as an alternative to enoxaparin in knee and hip replacement. Consequently, we do not presently need to compare apixaban to dabigatran in the prevention of venous thromboembolism associated with surgical procedures.

Symptomatic thromboembolism, and its prevention

In symptomatic thromboembolism, the Botticelli study has shown that apixaban had similar efficacy and safety to a LMWH followed by a Vitamin K antagonist.[23] This suggests that apixaban may be useful in symptomatic thromboembolism, as it is much easier to use than the combination of LMWH and Vitamin K antagonist eg, no subcutaneous injection, no monitoring of anti-coagulant effect and the expense associated with this. The Botticelli study is being followed-up by the AMPLIFY Phase III clinical trials,[25,26] and only when these studies are published will we have a definitive answer to whether apixaban is as efficacious and safe as the LMWH and Vitamin K antagonist combination in symptomatic thromboembolism.

Enoxaparin is the standard drug used to prevent thromboembolism in acute medical conditions including cancer, where the subject is immobilised. The ADOPT and ADVOCATE clinical trials have shown that apixaban is not superior to enoxaparin at preventing thromboembolism, but does increase bleeding in these subjects, compared to enoxaparin. Thus, apixaban should not be used to prevent symptomatic thromboembolism in acute medical conditions.

Recently, Kakkar et al have shown that enoxaparin does not give added benefit to elastic stockings with graduated compression, in acutely ill medical subjects.[35] As a possible explanation for this unexpected finding, Kakkar et al, suggested that

the natural history of deep-vein thrombosis may be different between subjects in hospital for medical conditions, and surgical procedures.[35] Consequently, enoxaparin and, possibly apixaban, could be less effective in thromboembolism associated medical conditions than surgical procedures. Apixaban is also not effective in preventing the thromboembolism associated with acute coronary syndromes.[36]

Conclusions

Apixaban should be considered as an alternative to replace enoxaparin in the prevention of thromboembolism associated with knee and hip replacement, because it is as efficacious as enoxaparin, but causes less bleeding. However, apixaban is not the only FXa inhibitor that could replace enoxaparin for this indication, as the FXa inhibitor rivaroxaban is as efficacious and safe as enoxaparin in preventing thromboembolism associated with these surgical procedures. Until the results of the AMPLIFY Phase III trial are known, it is too early to consider apixaban as an alternative to enoxaparin in symptomatic thromboembolism. Apixaban should not be used to prevent thromboembolism in medical immobilised subjects or subjects with acute coronary syndromes, as it has not been shown to be effective to date.

Author Contributions

Wrote the first draft of the manuscript: SAD. Made critical revisions and approved final version: SAD.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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