

Apixaban Versus Enoxaparin For Postoperative Thromboprophylaxis

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ABSTRACT

Background: Postoperative venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication following surgery. Pharmacological thromboprophylaxis is essential for reducing VTE risk. Enoxaparin, a low-molecular-weight heparin, is widely used, while apixaban provides an oral direct factor Xa inhibitor alternative. **Objective:** To compare the efficacy, safety, advantages, and limitations of apixaban and enoxaparin for postoperative thromboprophylaxis. **Methods:** Evidence from randomized controlled trials, comparative studies, systematic reviews, and clinical guidelines was reviewed, focusing on VTE prevention, bleeding outcomes, route of administration, renal function, treatment duration, and patient-related factors. **Results:** Apixaban demonstrated effective VTE prevention with efficacy and bleeding outcomes broadly comparable to enoxaparin, particularly after major orthopedic surgery. Its oral administration offers greater convenience than subcutaneous enoxaparin. **Conclusion:** Apixaban is an effective oral option in appropriately selected patients. Treatment should be individualized according to surgical procedure, thrombotic and bleeding risks, renal function, and current guidelines.

Keywords: Apixaban; Enoxaparin; Postoperative thromboprophylaxis; Venous thromboembolism; Deep vein thrombosis; Pulmonary embolism; Factor Xa inhibitor; Low-molecular-weight heparin.

INTRODUCTION

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), continues to be one of the principal causes of avoidable postoperative morbidity and death globally. Virchow's triad of endothelial damage, prolonged immobilization-induced venous stasis, and coagulation cascade activation all contribute to a hypercoagulable condition after surgical operations.¹ Postoperative VTE is especially common after large abdominal and oncologic operations, as well as major orthopedic surgeries including total hip arthroplasty (THA) and total knee arthroplasty (TKA). The probability of postoperative DVT in high-risk patients may surpass 40–60% in the absence of proper thromboprophylaxis, underscoring the need of efficient preventative measures.²

Pharmacological thromboprophylaxis, which dramatically lowers the frequency of thromboembolic events and enhances surgical outcomes, has emerged as a key component of perioperative therapy. Enoxaparin and other low-molecular-weight heparins (LMWHs) have long been considered the standard of therapy due to their favorable safety profile, consistent anticoagulant response, and shown effectiveness. Enoxaparin inhibits factor Xa and, to a lesser extent, thrombin (factor IIa) by increasing the activity of antithrombin III. Despite its extensive usage, patient adherence may be hampered by the requirement for subcutaneous administration, dosage modifications in cases of renal impairment, and injection-related pain, particularly following hospital discharge.³

By providing efficient oral substitutes for injectable anticoagulants, the introduction of direct oral anticoagulants (DOACs) has completely changed the postoperative thromboprophylaxis landscape. Without the need for antithrombin as a cofactor, apixaban, a selective, reversible direct factor Xa inhibitor, prevents the production of thrombin and the development of clots. Apixaban has been a popular choice for postoperative VTE prophylaxis because of its known pharmacokinetic profile, consistent dosage regimen, quick start of action, few food interactions, and absence of routine coagulation monitoring.⁴

The effectiveness and safety of apixaban in comparison to enoxaparin in patients having elective hip and knee replacement surgery have been assessed in a number of sizable randomized controlled studies, such as the ADVANCE clinical trial program.⁵ These trials have shown that apixaban maintains a similar or reduced risk of serious bleeding while offering equivalent or better protection against VTE.⁶ Additionally, the use of DOACs in suitable surgical populations is becoming more and more supported by revised worldwide guidelines and growing real-world data.⁷ However, the decision between apixaban and enoxaparin in clinical practice is still influenced by a number of criteria, including patient comorbidities, renal function, bleeding risk, cost, medication interactions, and operation type.⁸

The increasing use of oral anticoagulants in perioperative medicine necessitates a thorough assessment of the available data in order to inform evidence-based decision-making. Thus, the purpose of this review is to evaluate apixaban and enoxaparin critically in terms of their pharmacology, mechanism of action, safety, clinical effectiveness, guidelines, practical concerns, and involvement in postoperative thromboprophylaxis in various surgical situations.

POSTOPERATIVE VENOUS THROMBOEMBOLISM

Postoperative venous thromboembolism (VTE) is one of the most common and potentially life-threatening complications following surgery. It includes pulmonary embolism (PE), which happens when a thrombus dislodges and blocks the pulmonary arteries, and deep vein thrombosis (DVT), which is defined by thrombus development in the deep veins, primarily of the lower limbs.² If left untreated, DVT and PE together greatly increase surgical morbidity, extended hospital stays, higher medical expenses, and death. Postoperative VTE is still a significant problem despite improvements in perioperative care, especially for patients having significant orthopedic, abdominal, pelvic, oncologic, and trauma procedures.⁷

Virchow's triad—venous stasis, endothelial damage, and hypercoagulability—is the main explanation for the development of postoperative VTE. Long-term immobility during surgical operations frequently results in decreased venous blood flow and venous stasis. During surgery, the vascular endothelium is damaged by tissue stress, which exposes subendothelial collagen and activates coagulation factors and platelets. Furthermore, increased procoagulant factor synthesis, inhibition of endogenous anticoagulant mechanisms, and decreased fibrinolytic activity all contribute to the temporary hypercoagulable condition caused by surgery. These processes work together to significantly raise the risk of thrombus development in the postoperative phase.⁹

The kind of operation, the patient's features, and the administration of thromboprophylaxis all affect the frequency of postoperative VTE. With documented rates of asymptomatic DVT surpassing 40–60% in the absence of prophylaxis, patients having hip fracture surgery, total hip arthroplasty (THA), and total knee arthroplasty (TKA) are among the highest-risk categories.⁷ Due to the fact that cancer itself encourages a prothrombotic condition, major abdominal and pelvic cancer operations also carry a substantial risk. Older patients and those who have been immobilized for an extended period of time after surgery are much more at risk. It has been demonstrated that appropriate thromboprophylaxis can lower the incidence of postoperative VTE by over 50%, underscoring its vital significance in surgical treatment.¹

The risk of developing postoperative VTE is influenced by a number of procedure-related and patient-related variables. Advanced age, obesity, a history of VTE, inherited or acquired thrombophilia, active cancer, pregnancy, hormone replacement therapy, the use of oral contraceptives, chronic heart failure, chronic kidney disease, inflammatory disorders, and extended immobility are among the patient-related risk factors. The length and complexity of the treatment, the kind of anesthetic used, substantial tissue dissection, significant orthopedic surgeries, trauma surgery, and extended hospital stays are all considered procedure-related variables. Risk assessment models, like the Caprini Risk Assessment Model, are frequently used to categorize surgical patients based on their risk of VTE and to help choose the best preventative treatments.¹⁰

Clinically, postoperative DVT can cause unilateral leg edema, pain, tenderness, warmth, erythema, and discomfort in the calf; however, many patients are asymptomatic. abrupt onset dyspnea, pleuritic chest discomfort, tachypnea, tachycardia, hypoxemia, and, in extreme situations, hemodynamic instability or abrupt mortality are common symptoms of pulmonary embolism. Clinical probability evaluation is used in conjunction with imaging modalities, such as computed tomography pulmonary angiography (CTPA) for suspected PE and compression ultrasonography for suspected DVT. Because postoperative inflammation typically results in high levels, laboratory testing of D-dimer has limited value shortly following surgery, decreasing its specificity.⁸

One of the main goals of accelerated recovery after surgery (ERAS) programs is to prevent postoperative VTE.² Based on the patient's risk of bleeding and thrombosis, current worldwide recommendations suggest tailored thromboprophylaxis.

Mechanical prophylaxis, such as graduated compression stockings and intermittent pneumatic compression devices, and pharmacological prophylaxis, such as fondaparinux, low-molecular-weight heparins (like enoxaparin), unfractionated heparin, and direct oral anticoagulants (DOACs) like apixaban and rivaroxaban, are examples of preventive measures.⁷ While apixaban has developed as an effective oral option with equal effectiveness and safety in some surgical groups, enoxaparin has long been the benchmark comparator among these medicines.¹¹

Apixaban

Apixaban is an orally active, direct factor Xa inhibitor (DOAC) that selectively and reversibly inhibits free and clot-bound factor Xa, thereby preventing the conversion of prothrombin to thrombin and reducing fibrin clot formation.^{[12][13]} Unlike vitamin K antagonists, apixaban does not require routine coagulation monitoring because it has predictable pharmacokinetics and pharmacodynamics.^[14]

The oral bioavailability of Apixaban is approximately 50%, reaches peak plasma concentration within 3–4 hours, and has a half-life of about 12 hours, allowing twice-daily dosing. Elimination occurs through multiple pathways, including hepatic metabolism (primarily via CYP3A4), renal excretion, and biliary/fecal elimination.^[13]

Apixaban has become an important option for postoperative thromboprophylaxis following major orthopedic surgeries, particularly total hip replacement (THR) and total knee replacement (TKR), where patients are at a high risk of developing venous thromboembolism (VTE).^[15] The recommended dose for thromboprophylaxis after elective hip or knee replacement surgery is **2.5 mg orally twice daily**, initiated **12–24 hours after surgery**, provided adequate hemostasis has been achieved.^{[13][15]} The treatment duration is **10–14 days after knee replacement** and **32–38 days after hip replacement**.^[6]

Several randomized controlled trials have demonstrated that apixaban is at least as effective as low-molecular-weight heparins (LMWHs), particularly enoxaparin, in preventing postoperative deep vein thrombosis (DVT) and pulmonary embolism (PE).^{[15][6]} The ADVANCE clinical trial program showed that apixaban significantly reduced the incidence of VTE and all-cause mortality compared with enoxaparin while maintaining comparable rates of major bleeding.^{[15][6]} In addition, oral administration improves patient convenience, eliminates the need for injections, enhances treatment adherence after hospital discharge, and facilitates outpatient management.^{[13][7]} However, apixaban should be used cautiously in patients with severe renal impairment, significant hepatic disease, or concomitant use of strong CYP3A4 and P-glycoprotein inhibitors or inducers due to potential alterations in drug exposure.^{[12][13]}

Enoxaparin

Enoxaparin is a low-molecular-weight heparin (LMWH) derived from unfractionated heparin by depolymerization. It exerts its anticoagulant effect by binding to antithrombin III, thereby enhancing the inhibition of activated factor Xa and, to a lesser extent, factor IIa (thrombin).^{[12][13]} Compared with unfractionated heparin, enoxaparin has a more predictable anticoagulant response, longer half-life, higher bioavailability following subcutaneous administration, and lower risk of heparin-induced thrombocytopenia (HIT).^[14] Routine coagulation monitoring is generally unnecessary except in selected populations such as patients with severe renal impairment, obesity, pregnancy, or extremes of body weight.

Enoxaparin has long been regarded as the standard of care for postoperative thromboprophylaxis following major orthopedic surgeries because of its well-established efficacy in preventing DVT and PE.^[6] The commonly recommended prophylactic regimen is **40 mg subcutaneously once daily**, beginning approximately **12 hours before or after surgery**, or **30 mg subcutaneously every 12 hours**, depending on institutional protocols and regional guidelines. Dose adjustment is required in patients with severe renal impairment (creatinine clearance <30 mL/min), where **30 mg once daily** is generally recommended.^{[13][16]}

Clinical studies have consistently demonstrated that enoxaparin effectively reduces postoperative VTE compared with placebo and has served as the comparator in most pivotal DOAC trials.^{[6][15]} Despite its proven efficacy, prolonged use may be associated with limitations including the requirement for daily subcutaneous injections, injection-site pain, bruising, reduced patient adherence after discharge, and the potential development of HIT.^{[12][13]} Compared with oral anticoagulants such as apixaban, enoxaparin may be less convenient for extended outpatient prophylaxis, although it remains a preferred option in patients where oral anticoagulants are contraindicated or when rapid anticoagulant reversal may be necessary.^{[7][13][16]}

COMPARISON OF APIXABAN VERSUS ENOXAPARIN

Efficacy

Apixaban and enoxaparin are widely recommended anticoagulants for postoperative thromboprophylaxis following major orthopaedic surgeries, particularly total hip arthroplasty (THA) and total knee arthroplasty (TKA). Apixaban is an orally

administered direct factor Xa inhibitor, whereas enoxaparin is a subcutaneous low-molecular-weight heparin (LMWH). Both agents inhibit factor Xa, but through different mechanisms, thereby preventing thrombin generation and fibrin clot formation.^{15,17}

The Phase III ADVANCE clinical trial program demonstrated that apixaban was at least as effective as, and in some studies superior to, enoxaparin in preventing the composite outcome of asymptomatic or symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), and all-cause mortality after orthopaedic surgery. In the ADVANCE-2 and ADVANCE-3 trials, apixaban significantly reduced the incidence of VTE compared with enoxaparin without increasing major bleeding.^{17,6}

A meta-analysis of randomized controlled trials involving more than 14,000 patients confirmed that apixaban reduced the risk of total VTE and VTE-related mortality more effectively than enoxaparin while maintaining a comparable safety profile.¹⁸ Consequently, current international guidelines recognize apixaban as an effective alternative to LMWH for postoperative thromboprophylaxis after elective hip and knee replacement surgery.²

Safety

Both apixaban and enoxaparin have demonstrated favourable safety profiles in clinical practice. The incidence of serious adverse events, wound complications, hepatic dysfunction, and overall mortality is similar between the two agents when used at recommended prophylactic doses.^{15,17,6}

One of the major advantages of apixaban is its oral route of administration, eliminating the discomfort associated with daily subcutaneous injections and improving patient satisfaction and compliance. Additionally, apixaban does not require routine coagulation monitoring because of its predictable pharmacokinetic and pharmacodynamic properties.²

Enoxaparin remains a well-established anticoagulant with extensive clinical experience; however, dose adjustment is required in patients with severe renal impairment (creatinine clearance <30 mL/min), and prolonged use may rarely be associated with heparin-induced thrombocytopenia (HIT).⁷

Overall, both medications are considered safe for postoperative thromboprophylaxis when patient-specific risk factors, renal function, and bleeding risk are carefully assessed.^{2,7}

Bleeding Risk

Bleeding is the most clinically significant adverse effect associated with anticoagulant therapy. The balance between preventing thromboembolic events and minimizing bleeding complications is essential when selecting postoperative thromboprophylaxis.

Evidence from the ADVANCE trials demonstrated that apixaban did not increase the incidence of major bleeding compared with enoxaparin despite providing superior protection against VTE.^{17,6} Similarly, pooled analyses and meta-analyses reported comparable rates of major bleeding and clinically relevant non-major bleeding between the two agents.¹⁸

The randomized clinical trial conducted in women undergoing surgery for gynaecologic malignancies also demonstrated no statistically significant difference in major bleeding between apixaban and enoxaparin, supporting the favourable safety profile of apixaban beyond orthopedic surgery.¹⁸

Although both drugs have comparable bleeding risks, patient-related factors such as advanced age, renal impairment, concomitant antiplatelet therapy, previous bleeding history, and hepatic dysfunction should be considered before initiating anticoagulant therapy.^{2,7}

Clinical implication

Overall, apixaban provides effective thromboprophylaxis with a bleeding risk comparable to enoxaparin, making it an attractive option for patients requiring extended postoperative prophylaxis because of its oral administration and ease of use.^{2,17}

Clinical Evidence

The efficacy and safety of apixaban for postoperative thromboprophylaxis have been established through several high-quality Phase III randomized controlled trials collectively known as the **ADVANCE trial program**, as well as subsequent systematic reviews and guideline recommendations.

ADVANCE-1 Trial

The ADVANCE-1 trial compared apixaban 2.5 mg twice daily with enoxaparin 30 mg twice daily in patients undergoing total knee arthroplasty. Apixaban demonstrated similar efficacy in preventing VTE while showing fewer clinically relevant bleeding events, suggesting an improved benefit-risk profile.¹⁵

ADVANCE-2 Trial

The ADVANCE-2 trial evaluated apixaban against enoxaparin 40 mg once daily after total knee replacement. Apixaban significantly reduced the incidence of VTE and all-cause mortality without increasing major or clinically relevant bleeding.¹⁷

ADVANCE-3 Trial

In patients undergoing total hip arthroplasty, the ADVANCE-3 trial demonstrated that apixaban was significantly more effective than enoxaparin in preventing postoperative VTE and death from any cause while maintaining similar rates of major and clinically relevant bleeding.⁶

Meta-analysis of Randomized Controlled Trials

A comprehensive meta-analysis including more than 14,000 patients undergoing elective hip and knee replacement surgery concluded that apixaban significantly reduced total VTE and VTE-related mortality compared with enoxaparin, without increasing the incidence of major bleeding. These findings support the overall superiority of apixaban in terms of efficacy while maintaining comparable safety.¹⁸

Evidence in Non-Orthopaedic Surgery

The randomized clinical trial by Guntupalli et al. evaluated apixaban versus enoxaparin in women undergoing surgery for gynaecologic malignancies. The study found comparable rates of postoperative VTE and major bleeding between the two treatment groups, while patients receiving apixaban reported greater treatment satisfaction because oral administration avoided daily injections.¹⁸

Guideline Recommendations

The **American Society of Haematology (ASH)** and the **American College of Chest Physicians (ACCP)** recommend pharmacological thromboprophylaxis for patients undergoing major orthopaedic surgery and recognize direct oral anticoagulants, including apixaban, as effective alternatives to LMWH in appropriately selected patients.^{2,7}

CURRENT GUIDELINE RECOMMENDATIONS

Current clinical guidelines recommend that postoperative thromboprophylaxis should be individualized according to the patient's risk of venous thromboembolism (VTE), bleeding risk, type of surgical procedure, renal function, and expected duration of postoperative immobility. Pharmacological prophylaxis should generally be used when the risk of VTE outweighs the risk of bleeding, while mechanical methods such as intermittent pneumatic compression may be used alone when bleeding risk is high. [2,20]

For patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA), the American Society of Hematology (ASH) guideline recommends either aspirin or an anticoagulant for VTE prevention. When an anticoagulant is selected, a direct oral anticoagulant (DOAC) is suggested over low-molecular-weight heparin (LMWH). [2]

The National Institute for Health and Care Excellence (NICE) recommends pharmacological prophylaxis after elective hip or knee replacement when the risk of VTE exceeds the risk of bleeding. The choice of prophylactic treatment should be based on the surgical procedure and individual patient characteristics. [20]

For major general surgery, the ASH guideline suggests pharmacological prophylaxis with LMWH or unfractionated heparin. Similarly, for major gynecological surgery, LMWH or unfractionated heparin remains a recommended pharmacological approach. [2] Therefore, the choice of postoperative thromboprophylaxis should be based on the type of surgery and individual patient risk rather than applying a single anticoagulant strategy to all surgical populations.

The duration of prophylaxis should also be determined according to the procedure and individual VTE risk. Extended prophylaxis may be appropriate in selected patients undergoing major surgery, particularly when prolonged immobility or increased thrombotic risk persists. Mechanical prophylaxis may be considered in addition to pharmacological prophylaxis when appropriate and when bleeding risk permits. [2,20]

Overall, the choice between apixaban and enoxaparin should remain patient-specific and should consider renal and hepatic function, bleeding risk, drug interactions, adherence, route of administration, cost, and the indication for postoperative prophylaxis. [2,20]

CONCLUSION

Apixaban and enoxaparin are established options for postoperative VTE prophylaxis, particularly in surgical settings where pharmacological thromboprophylaxis is indicated. Current guidelines emphasize that the selection of an anticoagulant should be individualized according to the patient's VTE risk, bleeding risk, type of surgery, and other relevant clinical factors. [2,20]

The oral route of administration of apixaban may provide a practical advantage by avoiding subcutaneous injections. However, enoxaparin remains an established prophylactic option, particularly in surgical populations where LMWH is recommended by current guidelines. [2]

The choice of prophylactic agent should therefore not be based solely on the anticoagulant used but should take into consideration bleeding risk, renal and hepatic function, concomitant medications, type of surgery, duration of prophylaxis, and feasibility of postoperative administration. [2,20]

In conclusion, apixaban may represent an oral alternative to LMWH in appropriate postoperative settings; however, its use should be guided by the specific surgical indication, individual patient characteristics, and current clinical guideline recommendations. [2,20] Further clinical research is required to establish the role of apixaban across broader non-orthopedic surgical populations.

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