Venous thromboembolism prophylaxis in orthopedic surgery: a narrative review

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ABSTRACT

Venous thromboembolism (VTE) is a major complication of orthopedic surgery and can lead to complications including pulmonary embolism, stroke, or even death. This narrative review aims to summarize current approaches to VTE prophylaxis for patients undergoing orthopedic surgery while also considering current trends in research surrounding potential updates to clinical recommendations and establishing a clear case for the role of patient-centered therapeutic approaches when looking to manage orthopedic postoperative VTE and associated complications. A narrative review was performed based on existing literature published on the topic of VTE prophylaxis in orthopedic surgery between the dates 1.1.2012 and 12.31.2023. Articles were searched for using a combination of four key terms combined with Boolean operators and were searched for on three major databases – Google Scholar, PubMed, and ScienceDirect. Findings were combined with and compared to recommendations from major relevant professional organizations. A wide variety of guidelines for both chemoprophylaxis and mechanical prophylaxis were considered, with findings of particular interest being support for industry-standard low-molecular-weight heparin (LMWH) and direct oral anticoagulant (DOAC) chemoprophylaxis, along with increased interest in aspirin. The evidence also supports mechanical prophylaxis in conjunction with chemoprophylaxis. Given that few validated VTE risk prediction score calculators exist, it is the recommendation of the authors to enhance risk stratification and personalized medicine by developing an orthopedic-specific risk assessment model to assist in decision-making, risk factor identification, and overall provision of comprehensive, personalized care designed to optimize quality of life and maximize management of orthopedic postoperative thromboembolic complications.

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Introduction

With orthopedic surgical procedures growing to be some of the most common services provided in healthcare systems worldwide, venous thrombosis prophylaxis for patients undergoing orthopedic surgeries has gained more attention as a topic of active research and clinical trials.[1] Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a well-known adverse effect following orthopedic surgeries, both major and minor, that increases the risk of complications including greater short- and long-term mortality.[2] Major orthopedic surgery encompasses invasive procedures such as arthroplasty, spinal fusion, or fracture reduction and fixation, whereas minor orthopedic surgeries include less invasive, arthroscopic procedures or soft tissue repairs.[1] VTE complications include reduced mobility and limitations in walking or standing which may impact an individual's ability to perform tasks at work, participate in recreational activities, or engage in social interactions, consequently affecting independence and productivity, leading to decreased satisfaction with life.[3] In numerous studies, individuals with VTE

and VTE-related complications secondary to orthopedic surgeries were found to have reduced independence related to activities of daily living (ADLs) and quality of life (QoL) overall compared to control groups.[3-5] The aim of this narrative review is to summarize the current approaches to VTE prophylaxis for patients undergoing orthopedic surgery while also considering current trends in research surrounding potential updates to clinical recommendations and establishing a clear case for the role of patient-centered therapeutic approaches when looking to manage orthopedic postoperative VTE and associated complications.

Methods

This paper followed clear methods in the development of a narrative review looking at the major associations and organizations involved in providing recommendations for the betterment of the patient. On top of consulting the major organizations including, but not limited to, the American Society of Hematology, American College of Chest Physicians, and American Academy of Orthopedic Surgeons, the team looked at the major papers which have come out on the topics of guideline recommendations for venous thromboembolism prophylaxis in orthopedic procedures, aspirin as a prophylactic therapy option, and risk factors as it pertains to individual based care, from the period of 1.1.2012 to 12.31.2023. Papers were found utilizing four key search terms combined with Boolean operators. The final search was for "Venous Thrombosis Prophylaxis" AND "Orthopedic Surgery" AND "Total Joint Arthroplasty" AND "Aspirin As Prophylaxis" and this search was performed on three search engines Google Scholar, PubMed, and ScienceDirect. The main inclusion criteria were studies relevant to current thromboprophylaxis therapies in patients undergoing orthopedic surgery. Exclusion criteria included papers that did not have an English-language full text available, papers that have not yet been peer-reviewed, papers for which the peer-review status could not be determined, papers that were published in journals that are either not peer-reviewed or in which the peer-review status could not be determined, papers that were not deemed to be generalizable to the general patient population, and papers that were published before the year 2012.

The current guidelines

A myriad of papers and corresponding guidelines have established the accepted recommendations utilized worldwide for VTE prophylaxis in orthopedic surgery. Specifically, the most common guidelines are those published by American Society of Hematology (2019), American College of Chest Physicians (2012, updated in 2016 and 2021), American Academy of Orthopedic Surgeons (2011), and National Institute for Health and Care Excellence (2018), amongst various others (Table 1).[6-10] Throughout the mentioned organizations, the general consensus endorses the use of low molecular weight heparin (LMWH), direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), factor Xa inhibitors (fondaparinux), and aspirin (ASA), despite its historical skepticism, for patients undergoing total hip arthroplasty or total knee arthroplasty.[6-10]

Table 1. Summary of recommendations for VTE prophylaxis in orthopedic procedures.

Organization	Recommendations
American Society of Hematology	Total knee or hip arthroplasty Aspirin or DOAC over LMWH LMWH over warfarin Hip fracture Chemoprophylaxis over no prophylaxis
American College of Chest Physicians	Total knee or hip arthroplasty or hip fracture LMWH preferred to other chemoprophylaxis irrespective of mechanical compression use Knee arthroscopy without previous VTE No thromboprophylaxis Bleeding disorders Mechanical compression device *versus* no prophylaxis
American Academy of Orthopedic Surgeons	No risk Chemoprophylaxis and/or mechanical compression devices Previous VTE Chemoprophylaxis and mechanical compression devices Bleeding disorders Mechanical compression devices
National Institute for Health and Care Excellence	Lower limb immobilization LMWH or fondaparinux Fragility fractures LMWH or fondaparinux or mechanical compression devices if chemoprophylaxis is contraindicated Hip or knee arthroplasty LMWH with ASA or DOAC and mechanical compression Arthroscopic or foot/ankle procedures No thromboprophylaxis unless VTE risk outweighs bleeding risk

Role of aspirin

Historically, aspirin has been considered as second line prophylaxis for VTE prevention due its decreased efficacy compared to anticoagulants but increased efficacy against placebo.[11] However, aspirin offers numerous pragmatic advantages for preventing VTE, including being widely available, inexpensive, easy to take orally, and potential lower risk of bleeding complications than anticoagulant prophylaxis.[12,13] Recent studies and ongoing trials further investigate its potential benefits as a monotherapy *versus* hybrid therapy option for preventing VTE in patients undergoing orthopedic procedures and compare its efficacy and safety to traditional first line therapies like LMWH and DOACs.[12,14,15] Therefore, the guidelines recognize aspirin as an option for VTE prophylaxis in orthopedic procedures, although ultimately the chemoprophylaxis of choice is dependent on surgical procedure and patient comorbidities, as outlined within the guideline recommendations.

Pharmacologic VTE prophylaxis

Current research and clinical trials for VTE prophylaxis following orthopedic surgeries focus on several key areas (Table 2). Research aims to determine the optimal prophylactic treatment, including pharmacotherapy agents, dosing regimens, and duration of prophylaxis while minimizing the risk of bleeding complications. Studies such as those reviewed in the papers published by Matharu *et al*. and Singjie *et al*. continue to evaluate the efficacy and safety of different anticoagulants in preventing VTE in orthopedic surgery patients.[13,16] Overall, the studies found no statistically significant difference between anticoagulant comparators, including LMWH and DOACs, and aspirin as an alternate therapy. The conclusions found within the papers remain consistent with the recommended guidelines of LMWH and DOACs as the preferable prophylactic agents along with growing support for aspirin as a therapy of interest.

Mechanical VTE prophylaxis

Other papers published by Kwak *et al*. and Aprisundani *et al*. analyze clinical trials which compare various prophylaxis strategies, including mechanical compression devices, such as intermittent pneumatic compression, and early mobilization protocols in combination with pharmacological agents, to determine the most effective approach in different patient populations and surgical procedures.[28,29] The evidence supports mechanical prophylaxis in conjunction with chemoprophylaxis as a safe and ef-

Table 2. Commonly prescribed drugs for DVT prophylaxis post-surgery.

Drug name	Dose	Timing and duration
Low molecular weight heparin[10,17]	30 mg every 12 hours 40 mg every 24 hours	Start 6-12 hours post-surgery and then continue for 10 days with an additional 28 days of aspirin monotherapy afterwards Or Start 6-12 hours post-surgery and then continue for 28 days with mechanical VTE prophylaxis with compression stockings until time of discharge
Fondaparinux[18,19]	2.5 mg every 24 hours	Start 6 hours after surgery and continue for 28 days
Direct oral anticoagulants (DOACs)		
Apixaban[20,21]	2.5 mg every 12 hours	Total knee arthroplasty: 12-24 hours after surgery and then continued thereafter for 10-14 days
Rivaroxaban[21,22]	10 mg every 24 hours	Total knee arthroplasty: 6-8 hours after surgery and then continued thereafter for 10-14 daysTotal hip arthroplasty: 6-8 hours after wound closure and then continued for 3-39 days
Dabigatran[22,23]	110 mg or 220 mg once a day	Total knee arthroplasty: 220 mg once daily, started 6-12 h post-operatively, then 220 mg once daily for 12-15 days Total hip arthroplasty: 1-4 hours after surgery, then 220 mg once daily for 28-35 days
Edoxaban[24-26]	30 mg every 24 hours	Total knee arthroplasty: 6-24 hours postoperatively and continued for 7 days Total hip arthroplasty: 6-24 hour after surgery and continue for 11-14 days
Vitamin K antagonists (VKAs)		
Warfarin[18,19]	A therapeutic INR range of 2.0-2.5 (or 2.0-3.0 depending on the source) with dosing dependent on INR of the patient	1.0 mg per day starting seven days before surgery and was continued until a VTE event occurred or until 28±2 days
Platelet inhibitors		
Aspirin[27]	81 mg every 12 hours	Started on the evening of or the next day after the procedure and then continued for 4-6 weeks

fective method to reduce the risk of VTE and their related complications following orthopedic surgeries (Table 3).

Risk factors for VTE

Needless to say, individual risk factors, such as genetics, lifestyle, and environment, contribute to post-surgical complications including VTE. It is important to note that although the preexisting guideline recommendations differ depending on orthopedic procedure and some genetic predispositions, like clotting or bleeding disorders, they cannot account for all risk factors specific to each patient. Numerous studies have evaluated the relative significance of these risk variables in the therapeutic context, influencing the management of patients in a clinical setting.[30-32] In the systematic review by Horner *et al*., risk factors include history of thromboembolism, cardiovascular disease, geriatric age, and elevated BMI, amongst others.[30] Risk factors are grouped into modifiable *versus* non-modifiable categories. Modifiable risks are influenced by lifestyle or environment, giving the individual an opportunity to make alterations to decrease their risk. Contrarily, individuals are predisposed to non-modifiable risks, such as genetics, which increase the likelihood of developing VTE post-orthopedic surgery despite circumstantial adjustments. The growing interest in identifying patient-specific risk factors for VTE, both modifiable and non-modifiable, has served as a key impetus in the movement to develop personalized prophylaxis strategies. Surgical calculators have been developed to predict the risk of VTE after orthopedic surgery based on both modifiable and non-modifiable risk factors (Table 4); however, the accuracy of results vary between calculators. For example, one study found that the Caprini score had a higher accuracy than the Padua score for predicting VTE after total joint arthroplasty, with an accuracy of 94.1% compared to the Padua score's 47.9%.[33] However, other studies have found that the Caprini score is less accurate than other scores. For example, one study found that the Boston Medical Center VTE score was more predictive than the Caprini score, with a positive predictive value of 72.2% compared to the Caprini score's 51.2%.[34]

Breakthrough VTE

Despite the implementation of prophylaxis therapy, however, postoperative VTE occurrence in orthopedic surgery is not completely attenuated. VTE can occur despite prophylaxis because low doses of anticoagulants aim to strike a balance between reducing the risk of clot formation and minimizing the risk of bleeding complications. In surgical patients, higher doses of anticoagulants, while potentially more effective at preventing VTE, significantly increase the risk of bleeding during and after surgery. Therefore, the doses used for prophylaxis are deliberately kept lower to reduce these bleeding risks, acknowledging that this compromise might not fully eliminate the risk of VTE.[35,36] Regardless of preventive measures such as anticoagulant medications, mechanical compression devices, and early ambulation, VTE can still occur due to various factors inherent to orthopedic procedures, such as prolonged immobilization, tissue trauma, and manipulation of blood vessels. The systematic review conducted by Januel *et al.* found that the incidence of developing postoperative VTE in patients undergoing knee arthroplasty or hip arthroplasty increased from the post-surgical

Table 3. Indication for initiation and duration of various mechanical prophylaxis methods.[6,10,29,30]

Mechanical prophylaxis	Initiation	Duration
Intermittent pneumatic compression (IPC)	IPC devices can be placed on non-surgical leg at time of induction and on both legs after wound closure	Continue IPC device for 10-14 days post-operatively
Graduated compression stockings (GCS)	GCS can be initiated the day prior to surgery and continued post-operatively	Wear GCS day and night until no longer with significantly reduced mobility
Early mobilization	Total knee arthroplasty 4-8 hours post-operatively Hip fracture or arthroplasty 24-48 hours post-operatively	Partial or full weight-bearing activities(with limitations determined by the surgeon based on surgery)

Table 4. Examples of modifiable *versus* non-modifiable risk factors for VTE.[31-33]

Modifiable risk factors	Non-modifiable risk factors
Immobility	Geriatric age
Elevated BMI	Genetic factors Variants in factor V, prothrombin, fibrinogen gamma, hemophilia, or blood group non-O
Smoking/intravenous drug use	Comorbidities Cardiovascular disease Kidney disease Cancer
Medication	Prior thromboembolism

inpatient period to after hospital discharge despite receiving recommended prophylactic therapy.[35] While prophylaxis is crucial in mitigating VTE incidence, the persistent prevalence and increased risk highlighted in this article along with another published by Cote *et al*. elucidates the need for more effective risk stratification protocols and patient-specific risk estimates for individuals undergoing orthopedic surgeries.[36]

Factor XI and XIa inhibitors

Factor XI and Factor XIa inhibitors are the likely new breakthroughs coming in the next few years. Both of the current therapies are undergoing phase 3 trials at the point of the writing of this paper.[36] According to an article published in the Journal of the American College of Cardiology, these drugs have plans for both further non-inferiority and superiority trials in regard to their use as potential agents that would decouple hemostasis and anticoagulation.[37] Through the use of these drugs, it has been shown in Phase 2 trial data that they lower the risk of bleeding while improving the likelihood of preventing clotting.[37] The authorial team and larger scientific community eagerly await the phase 3 trial data at this time.

Conclusions and Future recommendations

At present, few VTE risk prediction score calculators exist and among these, errors have been identified, such as methodological issues and insufficient validation, which calls into question their impact on patient outcomes and physician decision making.[38] While some calculators, such as the Caprini Score, are validated tools for assessing VTE risk, some features limit their uses including lack of specificity, modifiability, subjectivity, or availability. Therefore, it is the authors' recommendation to enhance risk stratification and personalized medicine by developing an orthopedic-specific risk assessment model (RAM) to assist physicians with not only identifying correlating risk factors, but also with predicting an individualized mortality index in order to tailor thromboprophylaxis regimens accordingly.[39,40] Comprehensive care that shifts from a population approach to address personal contributing factors in VTE management is essential in optimizing quality of life. Overall, VTE is a prevalent concern in orthopedic surgery and the complexity of managing thrombotic complications in orthopedic settings requires a method for determining the most precise therapy tailored for each individual.

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