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Management of Venous Thromboembolism After Hip and Knee Arthroplasty

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Abstract

Venous thromboembolism (VTE), a term encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a leading cause of mortality following total hip arthroplasty (THA) and total knee arthroplasty (TKA). Optimizing thromboprophylaxis, or the prevention of VTE after surgery, is becoming increasingly critical as the demand and frequency of total joint arthroplasty rises globally. This review covers the current literature on the risk factors, detection, and prevention of VTE in patients undergoing THA and TKA. It compares the efficacy and safety profiles of the most common pharmacological interventions including aspirin, low molecular weight heparin, rivaroxaban, apixaban, and warfarin. Mechanical methods, such as pneumatic compression devices, as well as intraoperative considerations, such as anesthesia modality, operative time, and tourniquet time, are also discussed. Furthermore, this review explores recent surgical advancements including minimally invasive approaches and robotic-assisted THA and TKA. Despite advancements and extensive research, the optimal thromboprophylaxis regimen remains debated, which highlights the need for individualized, patient-centered approaches to thromboprophylaxis.

Keywords: Deep vein thrombosis; Minimally invasive surgery; Pharmacological thromboprophylaxis; Pulmonary embolism; Robotic assisted surgery; Total joint arthroplasty; Total knee arthroplasty; Total hip arthroplasty; Venous thromboembolism

Introduction

Total joint arthroplasty (TJA) is a commonly performed procedure designed to restore function and relieve pain in damaged or diseased joints by replacing them with prosthetic components. This intervention is most performed to address severe arthritis, fracture and degenerative joint diseases that impair quality of life [1]. Among the various types of joint replacement surgery, total hip arthroplasty and total knee arthroplasty are the most performed with osteoarthritis (OA) being the primary indication [2,3]. Despite the incredible success rates of these procedures, they do not come without risks.

Deep vein thrombosis (DVT), often leading to pulmonary embolism, remains one of the most common and serious complications associated with total joint arthroplasty and other conditions [4-10]. In THA specifically, the rate of lower extremity DVT has been reported to be as high as 19.78% and as low as 1.02% of cases [11,12]. This variation highlights the broad range of patient-related risk factors associated with postoperative DVT. Given these risks, the anticipated growth in the number of joint arthroplasties performed further underscores the importance of effective DVT prevention. Some studies predict the number of revision total hip arthroplasty (rTHA) procedures to increase by 42% by 2040 and 101% by 2060, as well a rise in revision total

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knee arthroplasty (rTKA) procedures by 149% by 2040 and 520% by 2060 [13-18]. This rise is mainly due to an aging population globally with an increase in life expectancy accompanied by increased prevalence of OA.

Given the rising demand of THA and TKA, addressing the associated risk of venous thromboembolism (VTE) is crucial to optimizing patient outcomes. Research efforts are focused on pharmacological, mechanical, and surgical methods for thromboprophylaxis [19]. This review aims to provide an overview of the current thromboprophylaxis measures that can be taken after total joint arthroplasty, with a particular focus on knee and hip arthroplasty, as well as to highlight current advancements in this area.

Surgical Background

Joint arthroplasty is generally divided into two categories: total joint arthroplasty (TJA) and partial joint arthroplasty, or hemiarthroplasty (HA) [20]. Total joint replacement entails removing all components of the damaged joint and replacing them with prosthetic materials. For example, total hip arthroplasty (THA) involves the replacement of the acetabulum of the pelvis as well as the femoral head, including parts of the proximal femoral shaft. When the acetabular cup does not need replacement, the procedure is then considered HA [21,22]. The choice of TJA over HA depends on patient-specific factors, including underlying pathology and long-term functional goals. Arthroplasties are further categorized into primary and revision arthroplasty, where primary revision refers to the first arthroplasty a patient receives in their lifetime while revision arthroplasty involves operating and modifying an existing prosthesis either because of implant wear over time or post-primary arthroplasty complications.

The materials used in prosthetics are crucial as the goal of joint replacement is for the implant to last as long as possible. There is potential for the body to reject implants which is mitigated by careful selection of the materials used to make prosthetic joint components. Most implants are made of metals such as titanium alloys and cobalt chromium [3]. The prosthetic components for THAs specifically are the ball and socket, which replace the femoral head the acetabular cup respectively, as well as the stem, which is a rod attached to the femoral component that fits within the medullary cavity of the femur, providing stability and proper weight distribution throughout the joint.

Equally important is the method of fixation whereby the prosthetic joint components are fixed in place allowing them to work effectively as a joint. With modern arthroplasty, the most common form of fixation has become cemented fixation, whereby polymethylmethacrylate (PMMA) cement is used to hold the implant in place [3]. Conversely, uncemented fixation relies on bone growth to permanently attach the prosthetic components to bone. Such prosthetics have recently undergone major advancements and are typically designed with specific surface components or materials that promote this bone growth process, such as porous metals [22-24]. Lastly, hybrid fixation integrates both techniques for maximal benefits, specifically in TKA whereby the tibial component is cemented, and the femoral component is not [25,26]. This fixation technique has shown to reduce post-operative loosening of prosthetic components, which is a common cause for revision arthroplasty. Ultimately, the best method of fixation depends on the type of procedure being done and specific patient factors, such as age [24,27]. For example, the benefits of cementless prosthesis include reduced operating time, increased bone stock preservation and improved integration of the implant, especially in younger and more active patients. However, regarding THA in patients aged 65 and older, several studies demonstrate lower rates of the need for revision arthroplasty after 1-2 years in patients who underwent cemented THA compared to the uncemented group, indicating decreased postoperative prosthetic complications [27,28]. Although rare, bone cement is associated with postoperative DVT through a phenomenon known as bone cement implantation syndrome [29-31]. However, this is typically not the sole reason to avoid cemented implants, as this decision relies on other patient-related factors.

Risk Factors and DVT Detection

Virchow's triad is a commonly used definition of the factors that lead to venous thromboembolism and clarifies why TJA increases the risk for developing venous thrombosis. This triad includes endothelial damage, hypercoagulability, and venous stasis [32-34]. Endothelial damage refers to trauma inflicted to the endothelial layer lining blood vessels, which can occur in veins during major orthopedic surgery such THA and TKA [32]. Furthermore, surgery and other trauma tends to put the body into a hypercoagulable state, increasing the risk for thrombus formation [32,35]. Lastly, venous stasis can occur due to damage inflicted to the valves within veins during surgery as well as tourniquet use [36,37]. Venous stasis also occurs postoperatively because of temporary immobility caused by TJA, which is why early mobility following surgery is ideal for DVT prevention [26]. Any condition that increases one of the three factors in Virchow's triad can theoretically increase the risk for developing DVT. There are several patient-related factors that further increase the risk for developing VTE following TJA, as shown in Figure 1.

Age

The most obvious of these factors is advanced age (>60 years) [36]. This is explained by the fact that venous compliance and fibrinolysis decreases with age while venous

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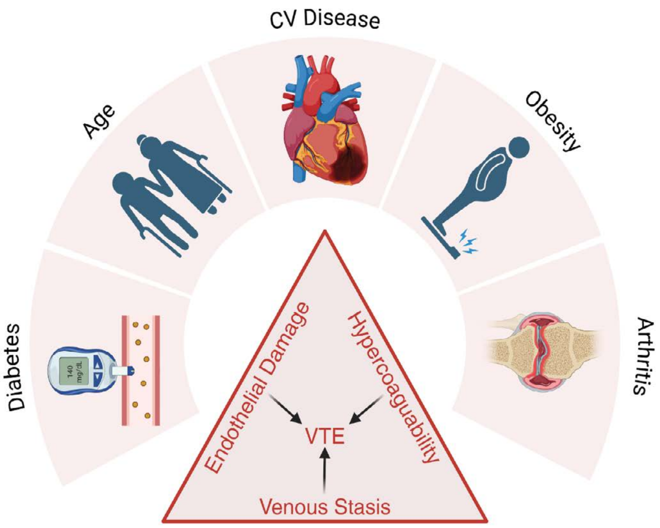

Figure 1: This figure depicts some of the most common risk factors contributing to venous thromboembolism as they relate to one or several aspects of Virchow's triad, displayed as the central pyramid. CV: Cardiovascular; VTE, Venous Thromboembolism

wall thickness increases [38]. On average, elderly individuals are also less mobile, increasing venous stasis, and have a higher risk of cardiovascular diseases that increase the risk of VTE.

Obesity

While the association of obesity with VTE after TJA is not very well established, there is some evidence to suggest that obesity increases the risk of VTE [39]. A study by Sloan et al. [40] found an increased risk of VTE after THA and TKA in patients with a BMI of at least 25 kg/m [40]. The proposed reasoning behind this increase is that obesity is correlated with increased operative times, lower mobility after surgery and reduced effectiveness of intermittent pneumatic compression (IPC) devices.

Diabetes

A meta-analysis by Yang et al. [41] found a statistically significant increase in DVT incidence following TKA in diabetic patients [41]. The proposed explanation behind this is that diabetic patients have abnormal mechanisms of coagulation, hemostasis and fibrinolysis, which promotes thrombus formation [42].

Arthritis

While osteoarthritis and rheumatoid arthritis are among the primary indications for THA and TKA, they are both associated with an increased risk of DVT following surgery, highlighting the need for careful preoperative management [2,3,32,34,36,43,44]. Both forms of arthritis can lead to immobility, increasing venous stasis and thus the risk for VTE [36,43]. In addition, the inflammation associated with rheumatoid arthritis can cause endothelial damage as well as increased hypercoagulability by upregulating procoagulants while downregulating fibrinolysis and anticoagulants [34].

Cardiovascular disease

Cardiovascular diseases such as congestive heart failure, atrial fibrillation and coronary artery disease, are known to increase the risk of VTE because of increasing venous stasis, endothelial injury and hypercoagulation [12,45,46]. Additionally, patients with cardiovascular diseases often require anticoagulant and antiplatelet medications, which can complicate thromboprophylaxis involved with TKA or THA [47,48]. TJA patients must discontinue the use of antiplatelet therapy 7-10 days prior to surgery to minimize the risk of excessive intraoperative bleeding [47]. This can become highly problematic for patients on anticoagulants because prolonged periods without their medication increases the risk for thrombotic events, myocardial infarction or cerebrovascular accidents [49]. Therefore, preventing lower extremity DVT and concomitant PE in patients suffering from cardiovascular diseases is a significant challenge.

Detection of DVT

There are several preoperative precautions that can be taken to mitigate the risk of developing DVT after total joint arthroplasty. One of the most common markers used to predict probability of DVT is a preoperative D-dimer test, as current research shows that increased D-dimer levels are associated with hypercoagulability and thus a higher risk of thrombosis [36,37,50]. Guo et al. [43] found that a preoperative D-dimer level greater than 0.585 µg/mL was significantly associated with an increased risk of DVT in patients undergoing TKA [43]. When used alongside D-dimer levels, ultrasonography is also an effective and commonly used tool to screen for DVT prior to surgery or for diagnosing DVT postoperatively [12,36,43,51]. These screenings can be utilized more frequently in high-risk individuals to detect DVTs before they embolize and cause catastrophic effects.

Although not typically used for the detection and prediction of DVT in patients undergoing TJA, some recent studies suggest that hematocrit (HCT) levels can predict the risk of developing DVT. For instance, Cong et al. [52] found that a HCT level less than 40% was a risk factor for DVT in older patients with hip fractures, like the value of 33.5% found by Li et al. [53]. Though these studies are focused on elderly patients admitted for hip fractures, their results can possibly implicate the use of HCT for the prediction of DVT risk surrounding THA and TKA. Another marker that has received some consideration as an early DVT predictor is the concentration of thrombin antithrombin complex (TAT) [54,55]. Specifically, a recent study by Lin et al. [54] examined the levels of TAT in patients following TKA and TJA [54]. They found a TAT level of 49.47 ng/mL in patients

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that developed DVT postoperatively and a level of 20.70 ng/mL in non-DVT patients. Similar to HCT, TAT can therefore be a possible predictor of VTE in patients undergoing TJA.

Thromboprophylaxis

To minimize the risk of postoperative VTE, administration of some form of thromboprophylaxis therapy is common practice following TKA and THA. Each potential technique discussed in this review is depicted in Figure 2 below. Aiming for early mobilization of patients in conjunction with a pharmacological thromboprophylaxis agent has proven to be effective at DVT prevention [56]. However, there is not one gold-standard guideline for physicians to follow and consequently there exists some disagreement surrounding the ideal method for thromboprophylaxis. This is currently the greatest challenge in managing the risk of DVT following TJA. The two most common guidelines that orthopedic surgeons follow, as seen in Figure 3A, are centered around meta-analyses conducted by the American Academy of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) [57,58].

One major difference between the two guidelines is the ideal mode of thromboprophylaxis. The AAOS guideline recommends the use of aspirin, low-molecular-weight heparin (LMWH), warfarin, or factor Xa inhibitors, such as rivaroxaban and apixaban [57]. The ACCP, on the other hand, primarily recommends LMWH as the ideal thromboprophylaxis agent following TJA because of its safety and efficacy, while recommending apixaban, rivaroxaban, aspirin, vitamin K antagonists (warfarin), or intermittent pneumatic compression devices as alternative treatments [58] (Figure 3B). The second significant difference between guidelines includes the timeline of thromboprophylaxis. While the AAOS does not specify a strict timeline for the initiation of treatment, it does recommend continuing prophylaxis for a minimum of 10-14 days postoperatively and extending this window to 35 days depending on patient risk factors [57]. The ACCP guideline also recommends the same duration and extension of thromboprophylaxis but recommends initiating LMWH treatment either 12 hours or more preoperatively or 12 hours more postoperatively [58]. Though these guidelines are helpful for physicians, there is still no consensus on the optimal thromboprophylaxis medication as they all have the potential to cause postoperative bleeding [59-61]. While aspirin is the most frequently used in the United States, its superiority over other options is not well established but has been a topic of extensive research in recent years.

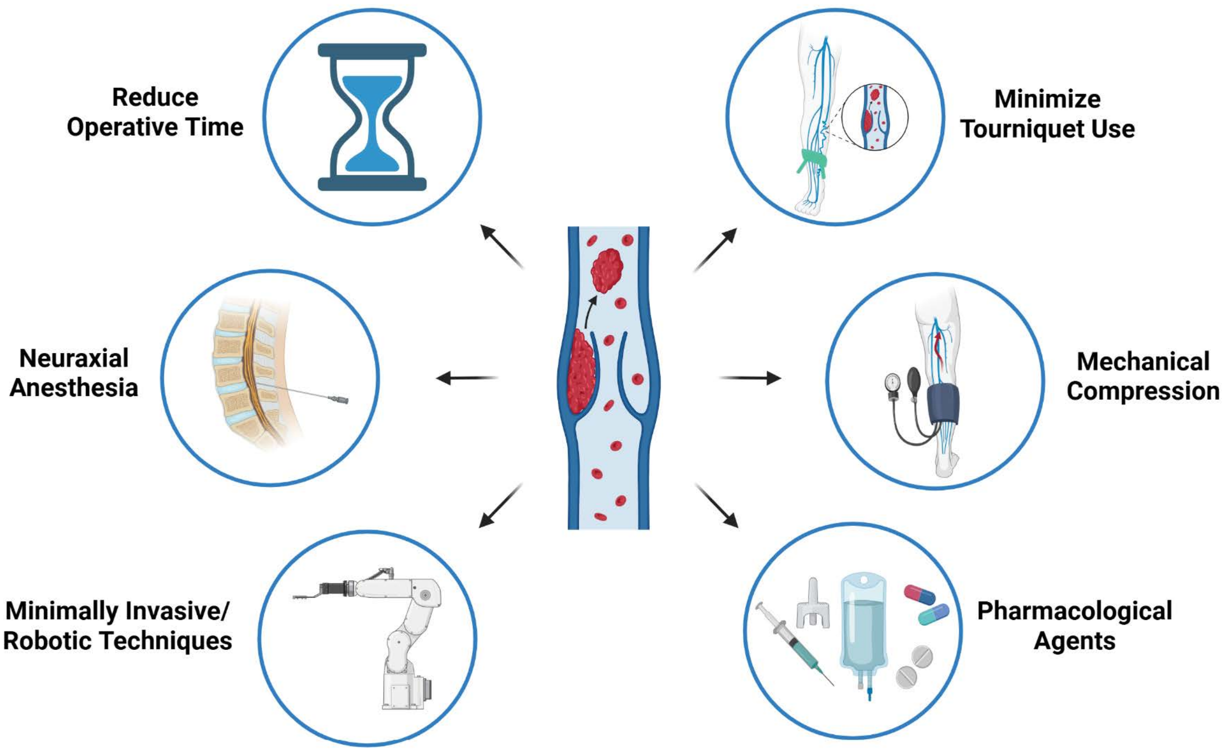

Figure 2: The image outlines the potential thromboprophylaxis techniques which can be incorporated into total hip arthroplasty and total knee arthroplasty procedures.

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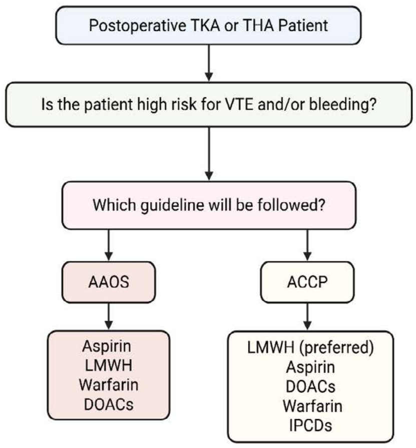

B

Anticoagulant	Pros	Cons/Avoid in Patients With...
DOACs (e.g., apixaban, rivaroxaban)	• Effective VTE prevention • No need for routine INR monitoring • Rapid onset and offset	• Severe renal impairment (CrCl <30 mL/min) • Severe hepatic impairment (Child-Pugh B or C) • Concurrent CYP3A4 or P-gp inhibitors • Mechanical heart valves • Baseline anemia or active cancer • Thrombotic antiphospholipid syndrome • High-risk bleeding surgeries
Aspirin	• Generally safe and well-tolerated • Widely available and inexpensive	• High bleeding risk • Concurrent anticoagulant use- Severe renal impairment (CrCl <30 mL/min) • Mechanical heart valves • Thrombotic antiphospholipid syndrome • High perioperative MI risk (↑ risk of nonfatal MI)
LMWH (e.g., enoxaparin)	• Effective VTE prophylaxis • Less need for monitoring (compared to warfarin)	• Severe renal impairment (requires dose adjustment) • Spinal/epidural anesthesia (risk of spinal hematoma)- Heparin or LMWH hypersensitivity
Warfarin	• Long-standing use • Preferred in mechanical heart valves and antiphospholipid syndrome	• Pregnancy (teratogenic) • Poor medication compliance • Need for regular INR monitoring • High bleeding risk- Narrow therapeutic window

Figure 3: **(A)** The flowchart depicts the most common approach and guideline to pharmacological thromboprophylaxis involved in total knee arthroplasty (TKA) and total hip arthroplasty (THA). **(B)** The strengths and weaknesses of using the anticoagulants that are discussed in the article, highlighting the importance of individualized care based on patient related risk factors. CrCl, creatinine clearance; DOACs, direct oral anticoagulants; INR, international normalized ratio; LMWH, low molecular weight heparin; MI, myocardial infarction; VTE, venous thromboembolism.

Pharmacological Methods

Aspirin

Aspirin is a popular choice for thromboprophylaxis as a monotherapy following THA and TKA because it is relatively cheap, well tolerated, does not require regular blood testing and exhibits minimal risks [62]. With direct oral anticoagulants becoming more common, there have been extensive efforts to reevaluate the efficacy and safety of aspirin compared to these drugs, such as rivaroxaban. Multiple meta-analyses of randomized clinical trials have shown equal effectiveness between Aspirin and other popular oral anticoagulants when comparing the rate of postoperative VTE in patients [62-68]. These studies determined safety by observing the rate of adverse events, such as bleeding, that occurred in patients while on treatment and found no statistically significant difference between aspirin and other treatments. In fact, the meta-analysis conducted by Matharu and colleagues [68] found lower rates of bruising in the Aspirin monotherapy group.

However, other studies showed conflicting results. The CRISTAL randomized trial specifically found symptomatic VTE in 3.45% and 1.82% of patients in the aspirin and enoxaparin treatment groups respectively [69]. These results and those of several other meta-analyses suggest that Aspirin is inferior in preventing VTE after TJA when compared to newer oral anticoagulants [69-72]. Though there are inconsistencies in the findings of Aspirin's effectiveness, one common conclusion among most of these studies is that Aspirin is equally as safe, if not safer, than other common oral

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anticoagulants (rivaroxaban and apixaban) when considering the risk of adverse effects such as bleeding [70-74].

Low Molecular Weight Heparin (LMWHs)

LMWHs, the most common being enoxaparin, is the thromboprophylaxis agent recommended by the American College of Chest Physicians (ACCP) guidelines [58]. Compared to aspirin, there seems to be less debate surrounding the efficacy of LMWH, with several systematic reviews and meta-analyses establishing that it is as effective at preventing VTE as newer direct oral anticoagulants [75-80]. Colwell et al. [75] highlight that the ACCP analysis showed a DVT prevalence of 33% with LMWH after TKA, which is reduced by about 50% compared to those without thromboprophylaxis [58,75].

While LMWH, such as enoxaparin, are highly effective thromboprophylaxis agents, they are also associated with increased postoperative risks, namely bleeding [19,79,80,81,82]. While the ACCP recommends the use of LMWH, they also highlight the increased bleeding rate of 2.4% [58,75]. A study by Wang et al. [81] reviewing patients undergoing TKA and THA in the US found a statistically significant increase of surgical site bleeding in LMWH treated patients (6.2%) compared to those given Warfarin (2.1%) (OR=3.82, 95% confidence interval [CI], 2.64 to 5.52) [81]. Despite the effectiveness of LMWH, careful consideration should be taken before administration as a prophylactic, especially in high-risk patients such as those with hemorrhagic disorders or gastrointestinal bleeding [83,84]. Further reasoning against LMWH use includes the fact that it is administered via daily subcutaneous injection, which some patients dislike due to the pain and injection site bleeding. This may lead to poor compliance in some patients.

Rivaroxaban and Apixaban

Rivaroxaban and apixaban are direct oral anticoagulants belonging to the class of antithrombotic drugs known as factor Xa inhibitors [85]. These compounds are commonly used for thromboprophylaxis following TJA and work by blocking the activity of factor Xa in the coagulation cascade, thus preventing blood clot formation.

The use of rivaroxaban following TJA is supported by the ACCP as well as multiple other studies [58,85-89]. A randomized, double blind study by Eriksson et al. [86] comparing THA patients treated with 10mg of rivaroxaban and 40mg of enoxaparin daily found a DVT incidence of 1.1% and 3.7% respectively (RR:0.26; 95% confidence interval [CI], 1.5 to 3.7; P<0.001) [86]. Furthermore, a meta-analysis by Huang et al. [87] demonstrated that rivaroxaban is associated with a statistically significant decrease in symptomatic DVT, asymptomatic DVT, symptomatic VTE, and proximal and distal DVT when compared to enoxaparin [87].

While rivaroxaban has been found to be a highly effective choice for thromboprophylaxis, the major concern surrounding its use is the risk of bleeding associated with it. Several studies have established that the risk of major bleeding after administration of rivaroxaban following TJA is comparable to that of enoxaparin [90-93]. Infact, a recent meta-analysis by Piple et al. [90] found a statistically significant increase in bleeding associated with rivaroxaban use compared to enoxaparin in both TKA and THA patients (TKA: adjusted odds ratio [aOR] = 2.58, P < 0.001; THA: aOR 1.64, P < 0.001) [90,91]. Furthermore, some data suggests that rivaroxaban is associated with other wound complications such as periprosthetic joint infections [92,93]. These findings warrant careful consideration of patient-related factors when choosing rivaroxaban as a thromboprophylaxis treatment.

Rivaroxaban and apixaban are similar in terms of their efficacy and safety profile and are often studied together. A study by Russel and Huo comparing the efficacy and safety of rivaroxaban and apixaban to enoxaparin found rivaroxaban and apixaban to be superior in preventing DVT following TKA [94]. Furthermore, there were no significant differences in associated bleeding between the drugs. Despite such findings, there are some studies suggesting differences between rivaroxaban and apixaban. For example, a study by Gomez-Outez et al. [95] found rivaroxaban to be associated with a higher risk of bleeding than apixaban with the two showing a similar risk of VTE [95]. Another study found that rivaroxaban was superior to apixaban in preventing overall VTE up to 35 days after THA in 2431 patients [96]. Therefore, while apixaban and rivaroxaban show similar efficacy and safety when used for thromboprophylaxis, rivaroxaban may have a slight edge in terms of preventing VTE while also having a lower safety profile.

Warfarin

While warfarin is a recommended form of thromboprophylaxis by the ACCP and AAOS, many studies suggest that it is not superior to other anticoagulants and may be associated with higher risks of bleeding than other antiplatelet therapies, like aspirin [57,58,97-100]. A meta-analysis by He et al. [97] found that warfarin displays a lower effectiveness for VTE prophylaxis following THA and TKA when compared to other oral anticoagulants such as rivaroxaban [97]. Those using warfarin also exhibited a higher rate of bleeding events in the 35 days following surgery. Another study conducted by Tan et al. [79] found that aspirin thromboprophylaxis resulted in a lower rate of DVT, overall VTE and PE compared to warfarin in both high-risk and non-high-risk patients [79]. Several other studies have found that aspirin was as effective if not more effective than warfarin at preventing VTE with a lower risk of bleeding in TKA and THA patients [97,99,100]. In addition, warfarin requires frequent blood monitoring which is inconvenient

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and costly. For these reasons, warfarin is not a popular choice for thromboprophylaxis following THA and TKA (used in 10% of TJA cases) [60,101].

Individualized pharmacological management

The most effective thromboprophylaxis for patients undergoing a total joint arthroplasty will require individualized assessments of their bleeding risk. Figure 3B summarizes the benefits and drawbacks to each thromboprophylaxis agent based on patient-specific risk factors. The most important factors include advanced age, (>65 years) renal impairment with creatinine clearance less than 50 mL/min, a history of major bleeding, concurrent use of antiplatelet therapy, low hemoglobin levels (<100 g/L) or baseline of anemia, significant liver disease such as cirrhosis, and active cancer, particularly involving the gastrointestinal or urogenital tracts [102-105]. In patients who have one or more of these risk factors, anticoagulant use should be done so with great caution.

Aspirin, which is generally safe, should be avoided in patients who have high bleeding risk or patients who are on another anticoagulant at the time of the procedure. The ASH guidelines recommend suspending aspirin to reduce the risk of bleeding complications in patients who are at high risk for bleeding or on a second anticoagulant, unless there is a recent acute coronary event or coronary intervention [58]. Aspirin should also be used cautiously in patients with severe renal impairment defined by low creatinine clearance (<30 mL/min). It should be avoided in patients with mechanical heart valves who will need more potent anticoagulants for safety measures and patients with thrombotic antiphospholipid syndrome. It should also be used carefully in patients with high perioperative myocardial infarction risk as aspirin may be associated with an increased risk of nonfatal myocardial infarctions [58].

Additionally, Low-molecular-weight heparins (LMWHs), although effective, require dose reduction and careful monitoring in patients with severe renal impairment (Creatinine clearance <30 mL/min) [106,107]. It should be used cautiously in those with spinal or epidural anesthesia due to risk of spinal hematoma [108]. The first dose should be delayed until after the epidural catheter has been removed, and the catheter should be removed 8 hours after the last dose of LMWH has been administered. Furthermore, LMWH should be avoided in patients with hypersensitivity to LMWH or heparin [106,107].

Warfarin, a teratogenic substance contraindicated in pregnancy, should be cautiously used in patients with poor compliance and increased risk of bleeding [58,107]. This medication requires frequent monitoring and dose adjustments due to its narrow therapeutic window and many patients have trouble adhering to regular monitoring of international normalized ratio (INR). Patients who have a history of atrial fibrillation who are already on Warfarin should stop the agent 3 to 5 days before surgery and typically will not require a bridging therapy [109].

Bleeding risk is a major factor when considering thromboprophylaxis, particularly with the use of direct oral anticoagulants (DOACs). While DOACs are effective in preventing venous thromboembolism (VTE), they should be used cautiously in patients with the bleeding risk factors above. In patients with severe renal impairment (creatinine clearance <30 mL/min), severe hepatic impairment (Child-Pugh B or C), those on strong CYP3A4 and P-glycoprotein inhibitors, those with mechanical heart valves, those with baseline anemia or active cancer, thrombotic antiphospholipid syndrome, and in specific perioperative contexts with high-bleeding procedures, other anticoagulants should be given before considering DOACs [106,110]. Ultimately, anticoagulation therapy in the context of arthroplasty should be tailored to each patient's unique clinical profile to maximize safety while effectively reducing the risk of venous thromboembolism [111].

Challenges and Future Direction in Pharmacological Thromboprophylaxis

Evidently, there is still much to learn about how these anticoagulants act as thromboprophylaxis agents following TKA and THA. Although newer, direct oral anticoagulants are convenient and effective at preventing VTE following TJA, they present a significant risk of bleeding. Given the current data, Aspirin seems to offer the lowest risk of bleeding, but whether it is as effective for thromboprophylaxis as drugs like rivaroxaban and apixaban is still not entirely certain. The differences in results between meta-analyses may be due to the heterogeneity within the individual studies chosen. For example, the dose administered, patient-related risk factors and follow-ups are some factors that are not controlled for between studies in many of the meta-analyses presented above. Therefore, making definitive generalizations about the most effective and safest method of thromboprophylaxis is challenging since the ideal prophylactic method depends on patient-related factors. A recent advancement in this field is the use of machine learning models to predict the risk of a patient developing VTE following TJA [112,113]. Although this field requires more development, these models may help physicians choose the best mode of thromboprophylaxis following THA and TKA, yielding better patient outcomes.

Mechanical Compression

Mechanical thromboprophylaxis refers to the use of intermittent pneumatic compression devices (IPCD) following TJA to prevent the development of VTE. Some observed benefits of mechanical compression are reduced

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lower extremity edema following TKA or THA as well as minimized risk for postoperative blood loss compared to treatments like enoxaparin [114-116]. Mechanical compression is recommended as an alternative treatment by the ACCP guidelines but is often used in conjunction with pharmacological thromboprophylaxis because its effectiveness in VTE prevention is not very well established [58]. A recent systematic review and meta-analysis found that IPCDs significantly reduced the risk of DVT and PE after surgery when compared to no thromboprophylaxis at all [117]. However, this study did not focus on patients who underwent TKA or THA specifically. Conversely, a study by Dietz et al. [118] found no significant difference in the rate of VTE in TJA patients receiving aspirin compared to those receiving a combination of aspirin and IPCD treatment [118]. They also point out the major challenge of compliance in patients using IPCD, stating that patient compliance within the first two weeks after hospital discharge was 51%. This is explained by the fact that the recommended daily usage of IPCDs is 18 hours, and it is not particularly comfortable for patients [58]. Therefore, IPCDs as a monotherapy for thromboprophylaxis following TJA should be carefully considered due to the lack of patient compliance and evidence supporting their efficacy. Further investigation is necessary to understand the effect of mechanical compression on the risk of VTE prevention following TKA and THA.

Intraoperative Thromboprophylaxis and Surgical Advancements

Operative time

Several studies have identified a correlation between increased operative times and increased risk for VTE following THA and TKA [12,39,119,120]. Yu et al. [12] specifically found that a surgery duration greater than 120 minutes was associated with a higher risk for postoperative DVT in patients undergoing THA [12]. This is explained by the fact that increased operative time increases the duration of venous stasis as well as the hypercoagulable state resulting from surgery, thereby increasing the risk for DVT according to Virchow's triad [32,33]. Thus, efforts to reduce operative time without sacrificing quality can be beneficial in the prevention of VTE associated with TKA and THA.

Anesthetic modalities

One of the intraoperative factors that may have a significant effect on the risk of VTE incidence after TJA is the type of anesthesia used during the procedure. The common modalities of anesthesia used during TJA include general anesthesia (GA), spinal anesthesia, epidural anesthesia and combined spinal epidural anesthesia (CSEA). Although GA is used most frequently in TJA (57.9%), some evidence suggests that GA, when compared to the other modalities, is associated with increased postoperative complications and mortality [121,122]. Diulus et al. [123] found that the odds of experiencing DVT was higher in THA and TKA patients who were given GA compared to those given spinal anesthesia (OR = 3.9; 95% CI: 1.2 to 17.3; P =0.04) [123]. Another study determined that neuraxial anesthesia, which encompasses spinal, epidural, and CSEA modes, was associated with a decreased 30 day DVT risk in THA patients compared to a GA group (OR= 0.63; 95% CI=0.4-0.9; P=0.02) [124]. Although many studies suggest that neuraxial anesthesia is equally as safe or safer than GA, it is not entirely certain which form of neuraxial anesthesia is best [121,124]. A study by Nakamura et al. [125] comparing combined epidural/general anesthesia and spinal anesthesia alone in TKA and THA patients found a 48% higher incidence of VTE in the spinal anesthesia group [125]. These results suggest that epidural anesthesia may have an advantage over spinal anesthesia. Although more research is needed to determine the relationship between anesthetic modality and postoperative VTE risk, opting for neuraxial anesthesia whenever possible in high-risk patients may be beneficial for thromboprophylaxis.

Tourniquet use

The use of a tourniquet during surgery has been studied as an intraoperative risk factor for DVT following TJA [126-128]. Although tourniquets are commonly used during TKA to minimize intraoperative blood loss, this is not the case for THA since the femoral head and acetabulum are located very deep in the pelvis, making tourniquet application difficult and possibly dangerous to the surrounding structures [36,129-132]. A meta-analysis by Ahmed et al. [126] found a postoperative DVT incidence of 3.4% in TKA patients who used a tourniquet vs 1.5% in the non-tourniquet group [126]. Similarly, Huang et al. [127] observed an increased early post-operative hypercoagulable state and incidence of below-knee DVT in the tourniquet group [127]. Although the bloodless field and reduced blood loss offered by tourniquet use can be ideal, it is important to consider the association with postoperative DVT when planning a TKA [36,133]. When a tourniquet is used, a possibly effective precaution that can be taken is minimizing the length of tourniquet time [134]. A study by Zan et al. [134] determined that releasing the tourniquet immediately after the prosthetic components are implanted was associated with a significantly lower risk of proximal DVT when compared to releasing after the application of dressings (4.6% vs 12%). Although these results are promising, there are minimal studies that demonstrate similar results. Therefore, more extensive research in this is needed to establish the association between tourniquet time and DVT incidence.

Minimally invasive approaches and robotic-assisted surgery

Though conventional TJA has become an incredibly successful procedure, there have been major advancements

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in minimally invasive surgical (MIS) approaches to TKA and THA within the past two decades [135]. These procedures aim to replace the targeted joint while minimizing the size of the incision made and the amount of muscle dissection during surgery [135-142]. Currently, the most widely used MIS approaches in THA are the minimally invasive anterolateral approach, direct anterior approach, and piriformis-sparing approach which all have the common objective of sparing musculotendinous structures such as the tensor fascia lata, piriformis muscle, and the gluteus medius and minimus muscles [135-137]. The predominant MIS techniques for TKA are the quadriceps sparing approach and the mini-medial parapatellar approach [138-140]. The proposed benefits of these MIS techniques include sparing of the extensor mechanism by preserving quadriceps muscle function, as well as decreased loss of blood supply to the joint. However, most studies demonstrate that MIS techniques do not directly reduce the risk of DVT following THA or TKA [143-145]. Theoretically, minimizing muscle damage through MIS may translate to earlier mobilization following surgery, thereby reducing the risk for DVT development. However, this connection has not been established and requires more extensive research.

Another recent advancement in the field of arthroplasty is computer-assisted navigation and robotic-assisted (RA) joint replacement whereby surgeons can use computer systems to more effectively and precisely plan and perform TJA and revision arthroplasty. Studies have consistently shown that RA joint replacement improves precision and accuracy of the prosthetic placement [146-150]. Clinically speaking, however, whether there is a reduction in postoperative VTE compared to traditional arthroplasty is yet to be determined. The few existing studies which investigate this correlation have determined that the risk of developing DVT after robotic assisted TKA and THA is lower when compared to traditional THA and TKA [151,152]. While this is promising, far more evidence is necessary to determine the relationship between postoperative DVT and RA TJA. Additionally, RA arthroplasty carries some risks of its own such as pin loosening [153,154].

Both RA and MIS are not highly favored and have not replaced traditional joint arthroplasty yet due to several factors, one of which is that they reduce the surgical window making it difficult to cement prosthetics accurately [138,139]. They also increase operative time, which can increase the risk for DVT as mentioned in an earlier section [12,39,40,119,120,155]. Overall, these techniques require specialized machinery, tools, and training [133]. Given the limited evidence of substantial benefits, the investment in these advancements may not yet be justified.

Conclusion

The prevention of DVT and concomitant PE in patients undergoing THA or TKA is complex and multifactorial. Pharmacologically speaking, each agent discussed comes with trade-offs in terms of efficacy and risks. Therefore, pharmacological thromboprophylaxis selection should balance efficacy with bleeding risks.

Aspirin is currently a widely used option, due to its low cost, ease of use, favorable safety profile, especially when it comes to its relatively lower bleeding risk [62-74]. It performs comparably to other agents, in standard-risk patients, though its efficacy in high-risk individuals is debatable. According to the CRISTAL trial and various meta-analyses, Aspirin has been slightly less effective at lowering the symptomatic VTE rates in comparison to other mainstay treatment options such as LMWH, with research showing 3.45% incidence of VTE using aspirin compared to 1.82% using enoxaparin [70].

Low-molecular-weight heparins are effective and reliable, especially in the hospital settings. However, they are associated with higher rates of surgical site bleeding and should be used with caution, particularly in high bleeding risk individuals, those with comorbid hemorrhagic disorders or history of gastrointestinal bleeding [19,79-84]. Warfarin, while still included in some guidelines, is less favored today due to its narrower therapeutic range, need for monitoring, and comparatively higher risk of bleeding and VTE.

Direct oral anticoagulants like rivaroxaban and apixaban offer convenient dosing and relatively the strongest VTE protection in patients compared to other mainstay pharmacological interventions including LMWH, with the DVT incidence of 1.1% and 3.7% respectively [86]. Furthermore, rivaroxaban has been associated with a statistically significant decrease in symptomatic DVT, asymptomatic DVT, symptomatic VTE, and proximal and distal DVT when compared to enoxaparin [87]. However, the research proves to be conflicting when considering how high the risk of bleeding is with DOAC use, especially with TJA. Some studies show DOACs having an equivocal risk for bleeding when compared with LMWH [90-93]. In contrast, a recent meta-analysis performed on patients undergoing TKA and THA showed a statistically significant increase in bleeding associated with rivaroxaban in comparison to enoxaparin, with an odds ratio of 2.58 [90,91]. Among the two DOACS studied, rivaroxaban and apixaban, apixaban may offer a slightly better bleeding profile with similar efficacy. In addition to the potential higher bleeding risk, rivaroxaban may be associated with increased wound complications including periprosthetic joint infections [92,93]. While DOACS are highly effective, it is important to use proper clinical judgement when selecting the best candidates, considering individual comorbid conditions and higher bleeding risk factors.

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In summary, aspirin remains the safest option regarding bleeding but may be less protective in high-risk scenarios. Rivaroxaban and apixaban are more potent but must be used cautiously due to bleeding complications. LMWH sits somewhere between these two options in accordance to bleeding risks, and warfarin is now used infrequently. Ultimately, the choice of agent should be tailored to the individual patient's thrombotic and bleeding risks. As predictive tools evolve, personalized thromboprophylaxis strategies will likely play a larger role in improving patient outcomes.

Mechanical thromboprophylaxis and intraoperative factors further aid in VTE prevention. The use of intermittent pneumatic compression devices (IPCD) has shown the ability to reduce lower extremity edema and postoperative blood loss compared to anticoagulant use like enoxaparin and promote improved outcomes when used in conjunction with medications [114-116]. Their effectiveness as a sole treatment remains limited due to issues with patient compliance, particularly after discharge, as the daily usage up to 18 hours is recommended for it to be effective and this is not comfortable according to patients [58].

Anesthesia also contributes to VTE outcomes, with neuraxial techniques being associated with a lower risk of postoperative DVT than with general anesthesia. While tourniquet use in TKA provides a bloodless surgical field and reduced intraoperative blood loss, it has been linked to a higher incidence of postoperative DVT when compared to non-tourniquet procedures, highlighting the importance to reduce tourniquet times.

Surgical approaches and practices also play a significant role in VTE prophylaxis. Because increased intraoperative times are associated with hypercoagulable states and prolonged venous stasis, the focus on newer modalities include efficiency and as minimally invasive techniques as possible. Recent advancements such as minimally invasive and robotic-assisted approaches aim to reduce tissue trauma and improve prosthetic precision; yet their benefits in reducing VTE incidence remain inconclusive, as increased operative times and technical challenges may offset their potential advantages. Collectively, these findings underscore the need for further research into integrated thromboprophylaxis strategies that consider both pharmacological and mechanical interventions, as well as intraoperative techniques, to optimize outcomes for patients undergoing TJA.

Key Points

- Total hip and knee arthroplasties are increasingly common procedures with high success rates but carry a significant risk of venous thromboembolism (VTE).
- Deep vein thrombosis (DVT) and pulmonary embolism (PE) are major postoperative complications that require proactive prevention strategies.
- Patient-specific risk factors such as age, obesity, diabetes, cardiovascular disease, and arthritis can elevate the likelihood of developing VTE after surgery.
- Preoperative screening tools like D-dimer tests and ultrasound imaging are useful for identifying patients at high risk for DVT.
- Aspirin is widely used in the U.S. for thromboprophylaxis due to its safety and low cost, but its effectiveness compared to other anticoagulants remains debated.
- Low molecular weight heparin (LMWH) is highly effective but carries a higher risk of bleeding and may reduce patient compliance due to injection-based delivery.
- Direct oral anticoagulants like rivaroxaban and apixaban are effective alternatives but also raise concerns over bleeding risks and wound complications.
- Mechanical methods, such as intermittent pneumatic compression devices (IPCD), can help reduce VTE risk but face limitations in patient compliance.
- Intraoperative factors like longer surgery duration, use of general anesthesia, and tourniquet application may increase DVT risk.
- Emerging techniques such as robotic-assisted surgery and machine learning risk prediction models offer promising avenues for improving individualized thromboprophylaxis.

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Consent for publication

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