

# Venous thromboembolism (VTE) prevention in orthopedics: facts, controversies, and evolving management

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**Abstract:** Multiple orthopedic procedures are performed each year including knee and hip replacements, also known as knee and hip arthroplasty. These procedures strongly activate the clotting cascade and increase the risk of venous thromboembolism (VTE). While everyone can agree that VTE is a serious and preventable problem following orthopedic surgery, not everyone agrees on best practice guidelines. This is compounded by the fact that there are multiple methods of VTE prevention including various chemoprophylactic and mechanical options as well as multiple organizations that have developed sometimes conflicting guidelines for VTE prevention including the American College of Chest Physicians and the American Academy of Orthopedic Surgery. The purpose of this paper is to present the available research on prominent chemoprophylactic VTE options for orthopedic surgery, examine and compare leading VTE prevention guidelines, and discuss the ramifications for noncompliance with industry standard guidelines.

**Keywords:** VTE prophylaxis, knee replacement, hip replacement

## Introduction

Each year more than 193,000 hip replacements and approximately 581,000 knee replacements are performed each year.<sup>1</sup> Orthopedic procedures strongly activate the clotting cascade and increase the risk of thrombosis by promoting endothelial injury during surgery and by enhancing venous stasis induced by immobility immediately following surgery. According to a study conducted by Spyropoulos et al, the rate of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) in United States orthopedic surgery patients was 4.7% with a median time of 51 days postsurgery.<sup>2</sup> However, the estimated incidence of DVT has been as high as 8.6% in a study of Asian patients who did not receive prophylaxis following total knee arthroplasty (TKA).<sup>3</sup> There are multiple prophylactic options for patients with several different opinions regarding best practice guidelines. The purpose of this paper is to present the available research on prominent chemoprophylactic venous thromboembolism (VTE) options for orthopedic surgery, examine and compare leading VTE prevention guidelines, and discuss the ramifications for noncompliance with industry standard guidelines. For the sake of brevity, this paper will focus on the most common orthopedic procedures – total hip and knee replacements.

## Prophylaxis options

There are several chemoprophylactic options for patients, including warfarin, low molecular weight heparin (LMWH), direct thrombin inhibitors, and selective Xa

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inhibitors, which each act differently to inhibit postoperative thrombosis. There is also a lot of debate surrounding optimal dosing and optimal postprocedure length of treatment; however, this will not be discussed in this paper. For each of these agents, it is important to consider the potential side effects, including bleeding risks, mechanism of clearance, comorbidities, and cost-effectiveness, when determining the best agent for each individual patient. Some of the differences among these agents are highlighted in Table 1.<sup>4</sup>

## Aspirin

Unlike the other prophylactic agents, aspirin is an antiplatelet agent that irreversibly inhibits cyclooxygenase, thereby inhibiting the production of thromboxane which normally allows platelets to group together near damaged blood vessel walls. However, aspirin inhibits both the cyclooxygenase-1 and cyclooxygenase-2 variant which not only inhibits the production of thromboxane but also the production of

prostaglandin, which normally plays a protective role in the gastrointestinal tract. This inhibition causes increased irritation of the gastric mucosa and increased propensity for bleeding. Aspirin is perhaps one of the most controversial antithrombotic agents in orthopedic procedures. Most of the controversy surrounds the level of evidence supporting aspirin as a sole chemoprophylactic agent. Part of the concern is the lack of evidence directly comparing aspirin to other chemoprophylactic agents. The most commonly cited trial is the PE Prevention trial which studied 13,356 patients undergoing surgery for hip fracture and 4088 patients undergoing elective arthroplasty who were randomized to receive either 160 mg daily aspirin or placebo for 35 days. In the hip fracture group, 1.6% of patients assigned to aspirin and 2.5% assigned to placebo had a DVT, PE, or both, which represents a proportional reduction of 36%.<sup>5</sup> Postoperative bleeding requiring transfusion occurred in 2.9% of aspirin users and 2.4% of those in the placebo group. In patients undergoing

**Table 1** Comparison of prophylactic agents<sup>4</sup>

Type of prophylaxis	Formulation	Other advantages	Other disadvantages	ACCP recommendation level
Mechanical			Not as effective prophylaxis used alone	1C for THA, TKA, or HFS. Recommended as 2C for dual therapy with antithrombotic agent. 2C as sole agent if increased bleed risk
Aspirin	Oral		Not high level of recommendation in all guidelines. May need further studies	1B for THA, TKA, or HFS
Warfarin	Oral		Requires extensive monitoring and lifestyle modification. Narrow therapeutic window	1B for THA, TKA, or HFS
Unfractionated heparin	Subcutaneous	Short half-life	Risk of developing heparin induced thrombocytopenia. Unpredictable dose response. Multiple daily injections	1B for THA, TKA, or HFS
Low molecular weight heparin	Subcutaneous	Less frequent dosing than unfractionated heparin and increased bioavailability		1B for THA, TKA, or HFS. Preferred over direct thrombin inhibitors, factor Xa inhibitors, and unfractionated heparin as 2B and over aspirin and warfarin as 2C
Factor Xa inhibitors	Subcutaneous		Needs to be dose adjusted for mild or moderate renal impairment and is contraindicated in severe renal impairment	1B for THA, TKA, or HFS. Apixaban is 1B as preferred oral agent
Direct thrombin inhibitors	Oral		Newer agent that may require further studies. Needs to be dose adjusted for mild or moderate renal impairment and is contraindicated in severe renal impairment	1B for THA, TKA, or HFS. 1B when oral agents preferred

**Notes:** American College of Chest Physicians grade 1 is a strong recommendation and grade 2 is a weak recommendation. Grade A implies high quality evidence (solid, plenty, convincing supportive data), B is moderate quality evidence (limited supportive data), and C is low or very low quality evidence (expert opinion or barely any supportive data). The 2011 American Academy of Orthopedic Surgery guidelines were not included in this table as they did not make specific recommendations regarding therapeutic agents. © 2012, American College of Chest Physicians. Reproduced with permission from the American College of Chest Physicians. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. *Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis*. 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl 2):7S–47S.<sup>4</sup>

**Abbreviations:** ACCP, American College of Chest Physicians; HFS, hip fracture surgery; THA, total hip arthroplasty; TKA, total knee arthroplasty.

elective knee or hip arthroplasty, PE or DVT occurred in 1.1% of patients in the aspirin group and 1.4% of patients in the placebo group. A prospective cohort study of 1947 patients who had total hip arthroplasty (THA) investigated a multimodal approach to prophylaxis that included aspirin or warfarin.<sup>6</sup> All patients received intermittent pneumatic compression (IPC) as soon as the patient arrived in recovery as well as knee-high elastic stockings, immediate active ankle flexion and extension exercises, and early ambulation on postoperative day one. In addition, 82.2% of patients received 325 mg aspirin and 17.8% received warfarin because of intolerance to aspirin, previous comorbidities, or high clinical risk for thromboembolic disease. In the aspirin group, 42/1599 patients (2.6%) developed DVT and 9/1599 (0.6%) developed PE. In the warfarin group, 14/348 (4%) patients developed DVT and 3/348 (0.8%) patients developed PE. Two patients who received aspirin and one who received Coumadin® (warfarin) had prolonged serous drainage that delayed their discharge, and one patient in the warfarin group had a major bleeding event. However, a study conducted by Lotke et al showed that there was no difference between aspirin and warfarin in bleeding complications or size and location of VTE.<sup>7</sup> A pooled analysis of randomized controlled trials conducted by Brown calculated the rates of venographic DVT, symptomatic DVT, PE, fatal PE, major operative site bleeding events, and major nonoperative site bleeding events.<sup>8</sup> There was no significant difference in clinically relevant outcomes between aspirin and LMWH or aspirin and pentasaccharides. There was, however, a higher rate of symptomatic DVTs in vitamin K antagonists compared with aspirin.

## Warfarin

Warfarin acts by inhibiting the vitamin K-dependent synthesis of clotting factors II, VII, IX, and X as well as protein C and protein S. When warfarin therapy is first initiated, it actually has a tendency to temporarily promote clotting activity because the normal levels of antithrombotic protein C and protein S are diminished. Therefore, warfarin is usually coadministered with another anticoagulant that acts on antithrombin to reduce the risk of thrombosis. In addition, it requires strict monitoring and diet/lifestyle modification in order to ensure the medication stays within its specified narrow therapeutic range. There is not much direct research on this agent; however, a meta-analysis of randomized trials evaluating chemoprophylactic methods including aspirin, LMWH, heparin, warfarin, dextran, and compression stockings to prevent VTE following total hip replacement showed that LMWH and warfarin were equally or more effective than all other treatments.<sup>9</sup>

## Heparin

Heparin binds to antithrombin III, thus inactivating thrombin and other factors in the clotting cascade such as factor X. Heparin can be administered as unfractionated heparin or LMWH, which is a more selective form with fewer side effects.

### Unfractionated heparin

Unfractionated heparin has several limitations including its variable antithrombotic response and the development of heparin-induced thrombocytopenia. Westrich et al studied high-risk patients undergoing THA to see if a single intra-operative dose of heparin prevents formation of DVT and determined that it does not prevent formation of pelvic thrombi; however, it was inconclusive in demonstrating effectiveness at preventing ipsilateral femoral thrombi.<sup>10</sup> Nurmohamed et al conducted a meta-analysis comparing LMWH with standard heparin for orthopedic surgery and general surgery patients.<sup>11</sup> In orthopedic patients, the mean incidence of DVT was 6.7% in patients receiving standard heparin and 5.3% in those receiving LMWH. The mean incidence of PE was 4.1% in the heparin group and 1.7% in the LMWH group, with a mean incidence of major hemorrhage at 0.9% and 1.3%, respectively. Another meta-analysis conducted about 18 years later also compared the effectiveness of unfractionated heparin with LMWH in both general surgery and orthopedic surgery.<sup>12</sup> However, because there is some concern of increased risk of bleed and heparin-induced thrombocytopenia, LMWH is generally preferred.

### LMWH

Enoxaparin is the most studied LMWH. There have been several studies comparing enoxaparin to placebo that have shown a relative reduction rate of venographically proven DVT following total hip replacement ranging from 0.5–0.63.<sup>13–15</sup> A meta-analysis of 22 studies comparing LMWH to unfractionated heparin and warfarin demonstrated that LMWH was better than unfractionated heparin and warfarin for the prevention of DVT, with a relative risk of DVT for LMWH versus unfractionated heparin of 0.76 and LMWH versus warfarin of 0.78.<sup>16</sup> LMWH had less bleeding complications than unfractionated heparin but more bleeding complications than warfarin. Another meta-analysis of randomized trials evaluating chemoprophylactic methods including aspirin, LMWH, heparin, warfarin, dextran, and compression stockings to prevent VTE following total hip replacement showed that LMWH and warfarin were equally or more effective than all

other treatments.<sup>9</sup> This same study showed LMWH was better than all other treatments at preventing DVT when risk estimates were adjusted for quality score.

## Factor Xa inhibitors

There are several agents that selectively inhibit factor Xa without affecting the other factors in the clotting cascade or platelets. There are two different administration methods: subcutaneous (fondaparinux) and oral (apixaban, rivaroxaban, and edoxaban).

### Fondaparinux

Fondaparinux is perhaps one of the most studied antithrombotic agents and several papers suggest that fondaparinux decreases the incidence of VTE following hip fracture surgery in both western and nonwestern countries.<sup>17–19</sup> There have been several trials comparing the effectiveness of fondaparinux versus mechanical prophylaxis alone and versus enoxaparin treatment. The PENTAMAKS (Pentasaccharide in Major Knee Surgery) trial studied patients undergoing elective major knee surgery and randomized them to receive 2.5 mg fondaparinux daily or enoxaparin 30 mg twice daily.<sup>20</sup> The primary outcome was VTE up to post-operative day eleven, which occurred in 12.5% of patients in the fondaparinux group versus 27.8% of patients in the enoxaparin group. However, major bleeding occurred more frequently in the fondaparinux group (2.1% versus 0.2%). The PENTHIFRA (Pentasaccharide in Hip-Fracture Surgery) trial studied patients undergoing hip fracture surgery and randomized them to receive either 2.5 mg fondaparinux once daily or 40 mg enoxaparin once daily.<sup>17</sup> The primary outcome was 8.3% and 19.1% in the fondaparinux and enoxaparin group, respectively, with a risk reduction of 56.4% with fondaparinux. By day 49, the incidence of symptomatic VTE was similar in both groups. The incidence of major bleed was also similar in both groups –2.2% in the fondaparinux group and 2.1% in the enoxaparin group. The EPHEBUS (European Pentasaccharide Hip Elective Surgery Study) trial studied 2309 patients undergoing elective hip replacement surgery who were randomized to either 2.5 mg fondaparinux or 40 mg enoxaparin daily.<sup>21</sup> By day eleven, 4% of patients in the fondaparinux group and 9% of patients in the enoxaparin group had VTE; by day 49, 1% of both groups had a symptomatic VTE with one fatality in the fondaparinux group from PE. The incidence of major bleed was similar in both groups. Lastly, the PENTATHLON (Pentasaccharide in Total Hip Replacement Surgery) study focused on 2275 patients undergoing elective hip replacement surgery

and randomized them to either 2.5 mg fondaparinux daily or 30 mg enoxaparin twice daily.<sup>22</sup> By day eleven, 6% of patients in the fondaparinux group and 8% of patients in the enoxaparin group developed VTE. The number of patients with major bleed also did not differ between the two groups. A worldwide study consisting of four randomized, double-blind trials in patients who underwent surgery for hip fracture, elective hip replacement, and elective major knee surgery was conducted to compare enoxaparin versus fondaparinux in preventing VTE. The overall incidence of VTE up to day eleven was reduced from 13.7% in the enoxaparin group to 6.8% in the fondaparinux group, with a relative risk reduction of 50.6% in favor of fondaparinux (95% confidence interval 40.9%–59.1%;  $P < 0.001$ ). The overall incidence of clinically relevant bleeding was low and did not differ between the two groups, and the benefit of fondaparinux was consistent across all types of surgery and all subgroups.<sup>23</sup> In addition, the PENTHIFRA-Plus (Pentasaccharide in Hip-Fracture Surgery Plus) trial, which was a double-blind randomized trial comparing 1 week of fondaparinux prophylaxis to 4 weeks of fondaparinux prophylaxis following hip fracture surgery, demonstrated that 4 weeks of prophylaxis reduced delayed VTE from 35% to 1.4% ( $P < 0.001$ ) without increasing the number of adverse events.<sup>23</sup> This suggests that extending prophylaxis to at least 4 weeks of fondaparinux may be preferable.

### Apixaban

Apixaban has also been compared to enoxaparin in three large-scale phase III trials – the ADVANCE (Apixaban Versus Enoxaparin for Thromboprophylaxis After Knee Replacement) trials – for the prevention of VTE in TKA (ADVANCE-1 and ADVANCE-2) and THA (ADVANCE-3). The primary outcome was total VTE events and all-cause mortality. In the ADVANCE-1 trial, 3195 patients were randomized to either 2.5 mg twice daily apixaban or 30 mg twice daily enoxaparin. The primary outcome was 9% in the apixaban group and 8.8% in the enoxaparin group, which did not meet noninferiority criteria. The rates of major VTE and all-cause death were similar in both groups (2.1% in the apixaban group and 1.6% in the enoxaparin group). Major bleeding occurred in 0.7% of apixaban patients and 1.4% of enoxaparin patients. The results of this trial suggest that apixaban and enoxaparin have similar effectiveness in thromboprophylaxis and lower rates of clinically relevant bleeding.<sup>24</sup> In the ADVANCE-2 trial, the dose of apixaban was the same but the dose of enoxaparin was only 40 mg once daily.<sup>25</sup> The primary outcome was 15.06% in the apixaban group and



24.37% in the enoxaparin group, with an absolute risk reduction of 9.27% in favor of the apixaban group. The rate of major bleed did not differ between the two groups, with nine major bleeds in the apixaban group and 14 in the enoxaparin group. Lastly, in the ADVANCE-3 trial, which consisted of 5407 randomly assigned patients, 3.9% of the enoxaparin group and 1.4% of the apixaban group achieved the primary efficacy outcome.<sup>26</sup> Major bleed during the treatment period occurred in 0.8% of patients who received apixaban and 0.7% of those who received enoxaparin. Overall, these results seem to indicate that apixaban is at least as effective as LMWH in preventing VTE in patients undergoing THA and TKA, and it has a similar risk for major bleed.

### Rivaroxaban

There have been four large-scale phase III trials comparing rivaroxaban to enoxaparin using similar endpoints as trials evaluating apixaban – the RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE) trials. Two trials assessed patients undergoing TKA (RECORD4 and RECORD3) and two trials assessed patients undergoing total hip replacement (RECORD1 and RECORD2). The RECORD4 trial consisted of 3148 patients undergoing TKA who were randomized to either 10 mg daily rivaroxaban or 30 mg twice daily enoxaparin.<sup>27</sup> The primary outcome occurred in 6.9% of patients in the rivaroxaban group versus 10% of those in the enoxaparin group. Major VTE occurred in 1.2% of patients with rivaroxaban and 2% of patients with enoxaparin. The rates of major bleed were similar in both groups (0.7% in the rivaroxaban group and 0.3% in the enoxaparin group). The RECORD3 trial also focused on patients undergoing TKA; however, instead of comparing rivaroxaban to 30 mg twice daily enoxaparin, it compared rivaroxaban to 40 mg daily enoxaparin.<sup>28</sup> The primary outcome occurred in 9.6% of rivaroxaban patients and 18.9% of enoxaparin patients. Major VTE occurred in 1% of rivaroxaban patients and 2.6% of enoxaparin patients. Again, the rate of major bleed was similar (0.6% of rivaroxaban patients versus 0.5% of enoxaparin patients). The RECORD1 trial consisted of 4542 patients undergoing THA randomized to 10 mg rivaroxaban or 40 mg daily enoxaparin.<sup>29</sup> The primary endpoint occurred in 1.1% of patients receiving rivaroxaban and 3.7% of patients receiving enoxaparin with major VTE in 0.2% of patients in the rivaroxaban group compared with 2% of patients in the enoxaparin group. Major bleed occurred in 0.3% of those receiving rivaroxaban and 0.1% of those receiving enoxaparin. The RECORD2 trial also studied patients undergoing THA; however, instead of

receiving enoxaparin and rivaroxaban for the same duration of 31–39 days as in previous trials, enoxaparin was given for a duration of 10–14 days and rivaroxaban was given for 31–39 days.<sup>30</sup> The primary endpoint occurred in 2% of patients in the rivaroxaban group and 9.3% of patients in the enoxaparin group, with major VTE in 0.2% and 2%, respectively. The incidence of major bleed was <0.1% in both groups. A pooled analysis of these four studies consisting of 12,729 patients demonstrated that the primary endpoint occurred in 0.5% of patients in the rivaroxaban group and 1% in the enoxaparin group, and major bleed occurred in 0.3% and 0.2%, respectively.<sup>31</sup> Overall, the pooled analysis demonstrated that rivaroxaban decreased symptomatic VTE and all-cause mortality after THA or TKA, with only a small increase in bleeding. However, another study that pooled data from three phase III multicenter clinical trials showed that while rivaroxaban had a two-fold lower risk of symptomatic VTE plus all-cause mortality, it also had a higher risk of bleeding (2.5% versus 3.1%).<sup>32</sup> Lastly, there is a study suggesting rivaroxaban may have the potential to reduce the cost of prophylaxis and the treatment of thromboembolic events following orthopedic surgery.<sup>33</sup>

### Edoxaban

Edoxaban is a newly developed oral direct factor Xa inhibitor. Raskob et al conducted a dose-response study which randomized 903 patients undergoing total hip replacement to receive edoxaban 15, 30, 60, or 90 mg once daily or subcutaneous dalteparin once daily given 6–8 hours postoperatively and continued for 7–10 days.<sup>34</sup> The primary endpoint, incidence of total VTE, occurred in 28.2% of patients receiving edoxaban 15 mg, 21.2% of patients receiving 30 mg, 15.2% of patients receiving 60 mg, and 10.6% of patients receiving 90 mg compared with 43.8% of patients receiving dalteparin. There was a low and similar rate of major bleed across the groups. A similar study was conducted in patients undergoing TKA that randomized 523 patients to receive either 5, 15, 30, or 60 mg daily edoxaban or placebo for 11–14 days.<sup>35</sup> The primary outcome was incidence of VTE and it occurred in 29.5%, 26.1%, 12.5%, and 9.1% in the edoxaban 5, 15, 30, and 60 mg treatment group, respectively, versus 48.3% in the placebo group.

### Direct thrombin inhibitors

Dabigatran is an oral direct thrombin inhibitor that was recently approved in 2010 by the Food and Drug Administration for stroke prevention in people with nonvalvular atrial fibrillation. While its efficacy in VTE prophylaxis

in the United States is still being evaluated, it was approved in Europe and Canada in 2008 for primary VTE prevention in knee and hip replacements. Dabigatran has been compared to enoxaparin in three large-scale phase III clinical trials for the prevention of VTE in THA (RE-NOVATE [Dabigatran Etxilate Compared With Enoxaparin in Prevention of VTE Following THA]) and TKA (RE-MODEL [Dabigatran Etxilate 150 mg or 220 mg Once Daily Versus Enoxaparin 40 mg Once Daily for Prevention of Thrombosis After Knee Surgery] and RE-MOBILIZE [Dabigatran Etxilate Versus Enoxaparin in Prevention of VTE Post Total Knee Replacement]).<sup>36</sup> In all three trials, the primary outcome was a composite of total VTE events (as measured by venographic or symptomatic DVT or PE) and all-cause mortality and the secondary outcome was major VTE plus VTE-related mortality. Both the RE-MODEL (Dabigatran Etxilate 150 mg or 220 mg Once Daily Versus Enoxaparin 40 mg Once Daily for Prevention of Thrombosis After Knee Surgery) and RE-NOVATE (Dabigatran Etxilate Compared With Enoxaparin in Prevention of VTE Following THA) trials demonstrated noninferiority for the primary outcome and RE-MOBILIZE (Dabigatran Etxilate Versus Enoxaparin in Prevention of VTE Post Total Knee Replacement) demonstrated noninferiority for the secondary outcome. In addition, there were no differences in the bleeding rates between the two treatments. The 8210 patients who participated in the three trials were later pooled for further analysis.<sup>37</sup> The pooled rate of major VTE or VTE-related mortality was 3.3% in the enoxaparin group versus 3% in the high-dose dabigatran (220 mg) group and 3.8% in the low-dose dabigatran (150 mg) group. There were seven VTE-related deaths. Six of them were in the dabigatran groups (two in the 220 mg group and four in the 150 mg group) and one in the enoxaparin group. The pooled rate of major bleed was 1.4% in the enoxaparin group versus 1.4% in the high-dose dabigatran group and 1.1% in the low-dose dabigatran group, and most of the major bleeding events occurred at the surgical site. There was a fatal bleed and a critical organ bleed in each of the two dabigatran treatment groups and none in the enoxaparin group. Lastly, in the RE-NOVATE (Dabigatran Etxilate Compared With Enoxaparin in Prevention of VTE Following THA) II trial, patients undergoing THA were randomized to either 220 mg dabigatran daily or enoxaparin 40 mg daily. The primary outcome occurred in 7.7% of patients in the dabigatran group and 8.8% of those in the enoxaparin group, and major bleeding occurred in 1.4% of dabigatran patients versus 0.9% of enoxaparin patients. These studies suggest that dabigatran administered at 220 mg daily has similar

efficacy and risk of bleeding as enoxaparin. To date, of the newer oral anticoagulants, only rivaroxaban has received Food and Drug Administration approval in knee and hip replacements.

## Mechanical

Mechanical prophylaxis includes the use of IPC, graduated compression stockings, and early mobilization. IPC externally compresses the lower limbs in a rhythmic fashion. Graduated compression stockings applies pressure to the lower extremity with a gradient pressure that is higher at the ankles and gradually decreases as it reaches the thigh or calf depending on the stocking length. Agu et al reviewed 15 randomized controlled trials of graduated compression stockings and found that stockings reduced the relative risk of DVT by 57% following total hip replacement and that chemoprophylactic agents such as heparin enhanced this effect.<sup>38</sup> Several studies have shown no difference between LMWH and IPC devices for hip fracture surgery and knee replacement surgery.<sup>39–43</sup> Studies comparing LMWH to IPC for patients undergoing THA found that none of the patients with a foot pump and 8% with LMWH developed a DVT.<sup>44</sup> However, there have also been some studies questioning the effectiveness of graduated compression stockings. Best et al found that 98% of stockings failed to produce the “ideal” pressure gradient, with overall risk of DVT at 16.7%.<sup>45</sup>

## Guidelines for prophylaxis

There are two major national guidelines governing VTE prophylaxis following orthopedic procedures – American Academy of Orthopedic Surgeons (AAOS) and American College of Chest Physicians (ACCP) – and one international guideline – International Consensus Statement on the Prevention and Treatment of VTE. Initially, there were multiple differences including recommended prophylactic agents and also whether or not patients should be risk stratified based on bleed risk prior to receiving prophylaxis. However, the new revised guidelines from both AAOS and ACCP are now more similar as ACCP has now taken into account bleed risk; however, there are still some differences in the recommended agents.

In 2007, AAOS developed recommendations based on risk stratification for PE. They recommended routine assessment of preoperative risk of major bleed and thrombosis and determining prophylaxis based on the risk-benefit ratio. If patients have a known contraindication to anticoagulation, then an inferior vena cava filter should be placed. For patients with standard risk of both PE and

major bleed, there are several chemoprophylactic options. First, aspirin either 325 mg twice daily or 81 mg daily to reduce gastrointestinal symptoms can be started the day of surgery and continued for 6 weeks. LMWH or synthetic pentasaccharides such as fondaparinux can be used starting 12–24 hours postoperatively and continued for 7–12 days. Lastly, warfarin can be started either the night before or the night after surgery and continued for 2–6 weeks. For patients with an elevated risk of PE and a standard risk of major bleed LMWH, synthetic pentasaccharides or warfarin can be used. The same recommendations also apply for patients with an elevated risk of both PE and major bleed. For patients with standard risk of PE and elevated risk of major bleed, aspirin and warfarin can be used. All patients should be considered for intraoperative and/or immediate postoperative mechanical prophylaxis until discharged home, and all patients should be considered for regional anesthesia as it has been shown to minimize decreased venous flow and leads to fewer pulmonary complications. Additionally, patients should be mobilized as soon as it is medically safe with attention to pain management to ensure early pain-free ambulation.

Recently in September 2011, AAOS released some updated recommendations regarding VTE prevention in patients undergoing knee and hip arthroplasty. They said that they could not recommend either for or against routine screening of patients for VTE risk factors besides prior VTE. In addition, they recommended assessing for presence of known bleeding disorder or active liver disease but could not recommend either for or against assessing for other bleeding risk factors. For patients without elevated risk of VTE or bleeding beyond that inherent in the surgery, they recommended the use of pharmacologic and/or mechanical devices but were unable to recommend any specific agents or duration of prophylaxis. Patients with prior history of VTE should receive pharmacologic prophylaxis and mechanical prophylaxis, and patients with bleeding disorder and or active liver disease should use mechanical devices. They continued to endorse early mobilization. They also recommended neuraxial anesthesia and they retracted their recommendation for the use of inferior vena cava filters in patients who have a contraindication to chemoprophylaxis or known VTE. These new guidelines, like the ACCP guidelines, assume that anyone undergoing THA or TKA is at elevated risk for VTE and bleed, and it further risk stratifies patients based on prior history of VTE, bleeding disorder, or active liver disease.

In February 2012, ACCP came out with revised guidelines for VTE prophylaxis in patients with orthopedic surgery.<sup>4</sup> According to the new guidelines, patients undergoing THA

or TKA can use LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K agents, aspirin, or IPC for a minimum of 10–14 days and for up to 35 days from the day of surgery in the outpatient period. For patients undergoing hip fracture surgery, they recommended use of LMWH, fondaparinux, low-dose unfractionated heparin, adjusted-dose vitamin K agents, aspirin, or IPC. Although there was a panel member who strongly believed that aspirin alone should not be used, it was included in the guidelines. While all of these agents can be used, LMWH is the preferred agent since there are limitations with the other agents including possible increased risk of bleed with fondaparinux, rivaroxaban, and vitamin K agents, possible decreased efficacy with low-dose unfractionated heparin, vitamin K agents, aspirin, and IPC alone, and lack of long-term safety data with the newer agents of apixaban, dabigatran, and rivaroxaban. However, the addition of these agents allows some flexibility for patients/physicians who are more concerned about avoiding bleeding complications or who may not tolerate intravenous or intramuscular formulations. If a patient prefers to not have injections or IPC, they recommend using apixaban or dabigatran (rivaroxaban or adjusted-dose vitamin K agents can be used if those agents aren't available) over other oral agents. For patients undergoing major surgery, they recommend dual prophylaxis with an antithrombotic agent and an IPC during their hospital stay. However, if a patient has an increased risk of bleed they suggest using an IPC or no prophylaxis as opposed to pharmacologic treatment. In addition, they recommend against using an inferior vena cava filter for primary prevention and are against routine screening with Doppler ultrasound of asymptomatic patients following orthopedic surgery. These recommendations differ from the previous guidelines of 2008 in multiple ways. First, the 2008 guidelines recommend against use of aspirin, unfractionated heparin, or IPC as the sole method of thromboprophylaxis, whereas these are satisfactory agents in the updated guidelines. In addition, LMWH is now the preferred agent for TKA, THA, and hip fracture surgery as opposed to just THA and TKA. In addition, they recommend extending prophylaxis in the outpatient period for up to 35 days as opposed to just 10–14 days. Lastly, the revised guidelines allow more flexibility and take into account other considerations patients and physicians may have when initiating chemoprophylactic therapy, eg, bleed risk and mode of delivery.

The International Consensus Statement on the Prevention and Treatment of VTE suggests that for elective hip replacement, LMWH or fondaparinux are preferred for in-hospital

prevention, although fondaparinux, oral anticoagulant therapy, IPC, or foot impulse technology combined with graduated elastic compression are grade A recommendations. Prophylaxis with LMWH should be initiated before or after the operation and fondaparinux should be started at least 6–8 hours after surgery. In both cases, prophylaxis should be continued for 4–6 weeks. An IPC device or foot impulse technology combined with graduated elastic compression stockings are an equivalent alternative to LMWH if there is concern about bleed risk and can be used as long as tolerated and then replaced with chemical prophylaxis for the rest of the 5-week period. For elective knee replacement, LMWH or warfarin (although less effective) are grade A recommendations, and fondaparinux is a grade B recommendation because of the increased risk of bleeding. Extending prophylaxis using LMWH to 30–42 days did not have as much of an effect on patients with total knee replacement as it did on patients with total hip replacement. An IPC device or foot impulse technology plus graduated elastic compression stockings are alternatives but need to be studied further. Lastly, for patients with hip fracture, LMWH, fondaparinux, adjusted-dose vitamin K agents (international normalized ratio range 2–3), or unfractionated heparin are grade A recommendations. IPC or foot impulse technology combined with graduated elastic compression should be used when pharmacologic prophylaxis is contraindicated. If surgery is to be delayed, prophylaxis should be initiated with LMWH, an IPC device, or foot impulse technology with graduated elastic compression as close to the fracture as possible.<sup>46</sup>

## Financial implications of postoperative VTE

Besides the medical and emotional complications of DVT, there is also a hefty financial cost. It has been estimated that the average discounted cost of DVT complications is \$3069.<sup>47</sup> In response to this, VTE following TKA and THA was added to the United States Centers for Medicare and Medicaid Services list of never events in August 2008.<sup>48</sup> This means that if a patient gets a VTE following either one of these procedures, Centers for Medicare and Medicaid Services can withhold a portion of payment for the procedure. However, as has been pointed out previously, this regulation overlooks the fact that VTE prophylaxis does not entirely prevent postsurgical VTE.<sup>49</sup> The authors also point out some unintended consequences of this rule including disincentivizing surgeons to perform knee or hip replacements particularly in high-risk patients, discouraging clinicians to pursue

objective radiological testing in the setting of suspected VTE, and encouraging overly aggressive prophylactic measures. In addition, physicians are penalized for the development of VTE even if they took necessary precautions and followed appropriate prevention guidelines. Another important issue is how to appropriately measure a VTE. Does this need to be done radiographically or can it be based on high clinical suspicion in cases where imaging may be contraindicated? In addition, is an asymptomatic DVT considered significant and will Centers for Medicare and Medicaid Services penalize physicians for these? It is a positive step in the right direction now that the ACCP and AAOS guidelines are more aligned, eliminating some of the confusion for clinicians in regards to appropriate VTE prophylaxis. However, despite physicians' best efforts at following these guidelines, there is still an inherent risk of VTE following these orthopedic procedures for which physicians may be penalized.

## Disclosure

Dr Jessica Langer has no conflicts of interest. Dr Alpesh Amin is a speaker and researcher with Boehringer-Ingelheim and Johnson & Johnson and a researcher with Pfizer and Bristol-Myers Squibb.

## References

1. AAOS.org [homepage on the Internet]. American Academy of Orthopedic Surgeons. 2012. Available from: <http://www.aaos.org/>. Accessed February 12, 2012.
2. Spyropoulos AC, Hussein M, Lin J, Battleman D. Rates of symptomatic venous thromboembolism in US surgical patients: a retrospective administrative database study. *J Thromb Thrombolysis*. 2009;28(4):458–464.
3. Chung LH, Chen WM, Chen CF, Chen TH, Liu CL. Deep vein thrombosis after total knee arthroplasty in Asian patients without prophylactic anticoagulation. *Orthopedics*. 2011;34(1):15.
4. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. *Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis*. 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(Suppl 2):7S–47S.
5. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355(9212):1295–1302.
6. Gonzalez Della Valle A, Serota A, Go G, et al. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. *Clin Orthop Relat Res*. 2006;444:146–153.
7. Lotke PA, Palevsky H, Keenan AM, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop Relat Res*. 1996;324:251–258.
8. Brown GA. Venous thromboembolism prophylaxis after major orthopaedic surgery: a pooled analysis of randomized controlled trials. *J Arthroplasty*. 2009;24(Suppl 6):77–83.
9. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA*. 1994;271(22):1780–1785.



10. Westrich GH, Salvati EA, Sharrock N, Potter HG, Sanchez PM, Sculco TP. The effect of intraoperative heparin administered during total hip arthroplasty on the incidence of proximal deep vein thrombosis assessed by magnetic resonance venography. *J Arthroplasty*. 2005;20(1):42–50.
11. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet*. 1992;340(8812):152–156.
12. Koch A, Ziegler S, Breitschwerdt H, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: meta-analysis based on original patient data. *Thromb Res*. 2001;102(4):295–309.
13. Planes A, Vochelle N, Darmon JY. Out-of-hospital prophylaxis with low-molecular-weight heparin in hip surgery: the French study-venographic outcome at 35 days. *Chest*. 1998;114(Suppl 2):125S–129S.
14. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty – the Danish Prolonged Prophylaxis (DaPP) study. *Thromb Res*. 1998;89(6):281–287.
15. Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med*. 1996;335(10):696–700.
16. Palmer AJ, Koppenhagen K, Kirchhof B, Weber U, Bergemann R. Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thrombo-embolism prophylaxis in orthopaedic surgery: a meta-analysis of randomized clinical trials. *Haemostasis*. 1997;27(2):75–84.
17. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med*. 2001;345(18):1298–1304.
18. Sasaki S, Miyakoshi N, Matsuura H, Saitoh H, Kudoh D, Shimada Y. Prospective randomized controlled trial on the effect of fondaparinux sodium for prevention of venous thromboembolism after hip fracture surgery. *J Orthop Sci*. 2009;14(5):491–496.
19. Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2003;163(11):1337–1342.
20. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med*. 2001;345(18):1305–1310.
21. Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet*. 2002;359(9319):1715–1720.
22. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet*. 2002;359(9319):1721–1726.
23. Turpie AG. Venous thromboembolism prophylaxis: role of factor Xa inhibition by fondaparinux. *Surg Technol Int*. 2004;13:261–267.
24. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med*. 2009;361(6):594–604.
25. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807–815.
26. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363(26):2487–2498.
27. Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009;373(9676):1673–1680.
28. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776–2786.
29. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358(26):2765–2775.
30. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2008;372(9632):31–39.
31. Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost*. 2011;105(3):444–453.
32. Huisman MV, Quinlan DJ, Dahl OE, Schulman S. Enoxaparin versus dabigatran or rivaroxaban for thromboprophylaxis after hip or knee arthroplasty: results of separate pooled analyses of phase III multicenter randomized trials. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):652–660.
33. Kwong LM. Cost-effectiveness of rivaroxaban after total hip or total knee arthroplasty. *Am J Manag Care*. 2011;17(Suppl 1):S22–S26.
34. Raskob G, Cohen AT, Eriksson BI, et al. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study. *Thromb Haemost*. 2010;104(3):642–649.
35. Fuji T, Fumita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. *J Thromb Haemost*. 2010;8(11):2458–2468.
36. Eriksson BI, Friedman RJ. Dabigatran etexilate: pivotal trials for venous thromboembolism prophylaxis after hip or knee arthroplasty. *Clin Appl Thromb Hemost*. 2009;15(Suppl 1):25S–31S.
37. Friedman RJ, Dahl OE, Rosencher N, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res*. 2010;126(3):175–182.
38. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg*. 1999;86(8):992–1004.
39. Blanchard J, Meuwly JY, Leyvraz PF, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br*. 1999;81(4):654–659.
40. Handoll HHG, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev*. 2002;4:CD000305.
41. Eskander MB, Limb D, Stone MH, et al. Sequential mechanical and pharmacological thromboprophylaxis in the surgery of hip fractures. A pilot study. *Int Orthop*. 1997;21(4):259–261.
42. Ginzburg E, Cohn SM, Lopez J, et al. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg*. 2003;90(11):1338–1344.
43. Knudson MM, Morabito D, Paiement GD, Shackelford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma*. 1996;41(3):446–459.
44. Pietsch M, Kuhle J, Hamer H, Pitto RP. Mechanical versus drug prevention of thrombosis after total hip endoprosthesis implantation. A randomized, controlled clinical study. *Biomed Tech (Berl)*. 2003;48(7–8):207–212. German.
45. Best AJ, Williams S, Crozier A, Bhatt R, Gregg PJ, Hui AC. Graded compression stockings in elective orthopaedic surgery. An assessment of the in vivo performance of commercially available stockings in patients having hip and knee arthroplasty. *J Bone Joint Surg Br*. 2000;82(1):116–118.

46. Nicolaidis AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int Angiol.* 2006;25(2): 101–161.
47. Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health.* 2003;6(1):59–74.
48. Deep vein thrombosis/pulmonary embolism. *Fed Regist.* 2008;73(161): 48480–48482.
49. Streiff MG, Haut ER. The CMS ruling on venous thromboembolism after total knee or hip arthroplasty: weighing risks and benefits. *JAMA.* 2009;301(10):1063–1065.

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