

DVT Prophylaxis in Total Joint Reconstruction

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KEYWORDS

- Prophylaxis • Deep venous thrombosis
- Venous thromboembolism • Total joint arthroplasty

Deep venous thrombosis (DVT) is the end result of a complex interaction of events including the activation of the clotting cascade in conjunction with platelet aggregation. It has been clearly demonstrated that patients undergoing major lower extremity orthopedic surgery, especially total joint arthroplasty (TJA), are at high risk for developing a postoperative DVT or a subsequent pulmonary embolus (PE). In the arena of TJA, orthopedic surgeons are particularly concerned with proximal DVT and symptomatic or fatal PE.

Patients undergoing primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) have exhibited rates of symptomatic PE as high as 20% and 8%, respectively when no prophylaxis has been administered.¹ As a result, the use of venous thromboembolic (DVT and PE) prophylaxis, most commonly pharmacologic prophylaxis, has become the standard of care for patients undergoing elective TJA. The risk of fatal PE following primary hip or knee replacement has been consistently reported to be between 0.1% and 0.2%, regardless of the chemoprophylactic agent employed for prophylaxis.²⁻⁹

Based on the necessity of postoperative venous thromboembolic (VTE) prophylaxis following TJA, the National Quality Forum endorsed a voluntary consensus standard for inpatient hospital care in

the earlier part of this decade. The surgical care improvement project (SCIP) guidelines, a result of the consensus, require documentation of initiation of DVT prophylaxis in the time period extending from 24 hours before surgery to 24 hours following surgery.¹⁰ The rationale for the SCIP guidelines stemmed from the government's emphasis on pay-for-performance (P4P) whereby physicians receive increased compensation as a function of meeting certain "standards of care."¹¹

Despite several years of evaluating this question, the best prophylaxis for thromboembolic disease remains controversial.¹² The use of pharmacologic prophylaxis has been adopted as the standard of care for treatment of these patients by many orthopedic surgeons at most centers across North America.¹³ However, the controversy between the efficacy of VTE prophylaxis and the increased risk for bleeding in the postoperative period continues to exist. In recent years, this debate has brought about the development of clinical guidelines to improve patient care, address key questions, define evidence-based recommendations, and promote future research. Clinical guidelines are not meant to represent a predefined protocol or absolute rules for treatment, and should never substitute for clinical judgment.

The authors have not received any financial support for the work and have no other financial or personal connections to the work presented in this article.

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Orthop Clin N Am 41 (2010) 273-280

doi:10.1016/j.ocl.2010.02.001

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Dependent on the clinical guideline followed, from the American College of Chest Physicians (ACCP) or the American Academy of Orthopaedic Surgeons (AAOS), there are several recommended regimens available for treatment. Included in the options are low molecular weight heparins (LMWHs), synthetic pentasaccharides, adjusted-dose warfarin, aspirin, and mechanical prophylaxis. Several studies have evaluated the various modalities for DVT prophylaxis, and comparison studies have stratified the risks and benefits for each option.

The following review addresses the controversy underlying VTE prophylaxis by outlining 2 guidelines and demonstrating the pros and cons of different DVT prophylaxis regimens based on the available evidence-based literature.

AMERICAN COLLEGE OF CHEST PHYSICIANS GUIDELINES

The ACCP was founded in 1935, and the first set of guidelines for venous thromboembolic prophylaxis (VTE) was published in 1986. The goal of these guidelines is to focus on the prevention of the overall rate of VTE. These guidelines are based on a review of prospective, randomized studies only. The guidelines have subsequently gone through several iterations with the most recent update in 2008.¹³ Inherent to these guidelines is that all primary THA and TKA patients are considered “high risk” regardless of patient age, activity level, and comorbidities.

These guidelines have become commonplace in the evaluation of health care systems on behalf of hospitals, insurance companies, and attorneys. The recommendations were classified as Grade I (strong recommendation, with benefits outweighing risk, burden, and cost) or Grade II (recommendation with less certainty). Each class of recommendation was further substratified: (A) randomized controlled trials with consistent results and a low level of bias, (B) randomized controlled trials with inconsistent results or a major methodological design flaw, and (C) observational studies.¹³ The use of LMWH, fondaparinux (pentasaccharide), and warfarin (with an adjusted international normalized ratio [INR] between 2.0 and 3.0) all received a Grade IA recommendation for preventative treatment of total hip and knee arthroplasty; aspirin or low-dose unfractionated heparin received a Grade IA rating against their use for prophylaxis in patients following TJA. The use of intermittent pneumatic compression devices received a Grade IB rating for prevention in patients undergoing TKA.

These guidelines also address the duration of prophylaxis. During the first iteration, the ACCP

guidelines from 1998 and 2001 recommended 7 to 10 days of prophylaxis that coincided with the length of hospital stay (Grade IA recommendation).¹⁴ In 2004, the guidelines were revised to recommend out of hospital prophylaxis for 28 to 35 days (Grade IA) but excluded patients undergoing TKA.¹⁵ With additional revisions, the 2008 guidelines currently recommend duration of prophylaxis with LMWH, fondaparinux, and warfarin for up to 10 days following THA and TKA (Grade IA), and up to 35 days following THA (Grade IA) or TKA (Grade IIB).¹³

As with any guidelines being used to guide physicians in medical decision making, the risk versus benefit must be assessed. Implementation of the current ACCP guidelines has been associated with certain disadvantages, as reported in the orthopedic literature. Burnett and colleagues¹⁶ reported a 4.7% readmission rate, 3.4% irrigation and debridement rate, and 5.1% rate of prolonged hospitalization following 10 days of LMWH after TJA. Parvizi and colleagues¹⁷ have shown that patients with a wound hematoma or persistent wound drainage are at higher risk for a postoperative deep joint infection. As a direct consequence of the concerns for postoperative bleeding risk and potential for infection, orthopedic surgeons may prefer a more risk-averse method by which to prevent thromboembolic phenomena following TJA, especially because the rate of PE is similar regardless of the chemoprophylaxis agent used.

AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS GUIDELINES

A work group from the AAOS in conjunction with the Center for Clinical Evidence Synthesis (Tufts New England Medical Center) proposed a new set of guidelines for the prevention of symptomatic and fatal PE in patients undergoing elective TJA. The AAOS guidelines are a synthesis of an expert consensus as well as an analysis of 42 articles published since 1996, and focus on the prevention of symptomatic PE. The clinical outcomes of choice for evaluation included symptomatic and fatal PE, death, and major bleeding episodes following TJA.¹⁸ Consensus recommendations included the use of regional anesthesia, mechanical prophylaxis for all patients, rapid postoperative mobilization, and adequate patient education. Each patient required a preoperative evaluation for a determination of “standard” and “high” risk potential. The choice of a specific chemoprophylaxis agent was based on the individual risk-benefit profile for PE and bleeding complication.

Each recommendation was graded using the following system: (A) good evidence (level I studies

with consistent findings) for recommending intervention, (B) fair evidence (level II or III studies with consistent findings) for recommending intervention, and (C) poor-quality evidence (level IV or V) for recommending intervention¹⁸ (Table 1). Of the total number of recommendations from this set of guidelines, only 4 of them were derived from a systematic review of the literature. Additional general consensus recommendations are listed in Table 2.¹⁸

For patients at standard risk for both PE and major bleeding complications, the recommendation is as follows: aspirin, LMWH, pentasaccharide, or warfarin (INR goal of ≤ 2.0). This recommendation is based on level III evidence and was given a grade of B or C.

For patients at elevated risk for PE and standard risk for major bleeding complications, the recommendation is as follows: LMWH, pentasaccharide, or warfarin (INR goal of ≤ 2.0). This recommendation is based on level III evidence and was given a grade of B or C.

For patients with standard risk of PE and elevated risk of major bleeding complications, the recommendation is as follows: aspirin, warfarin (INR goal of ≤ 2.0), or none. This recommendation is based on level III evidence and was given a grade of C.

For patients with elevated risk of both PE and major bleeding complications, the recommendation is as follows: aspirin, warfarin (INR goal of ≤ 2.0), or none. This recommendation is based on level III evidence and was given a grade of C.

The most important concept that is fundamental to the AAOS guidelines for thromboembolic prophylaxis is that the risk versus benefit for each individual patient must be assessed in the preoperative period. The general recommendations presented in Table 2 are a result of the work group's consensus, and address a majority of the perioperative issues with prophylaxis. For patients with elevated risks for PE, major bleeding complication, or both, these guidelines provide an effective manner by which to treat these patients in the postoperative period following TJA. However,

a weakness inherent to the AAOS guidelines is the inability to accurately assess the preoperative risk for DVT/PE. In reality, based on the nature of TJA, arthroplasty patients may not truly be considered low risk. In addition, there are studies to demonstrate rates of VTE as high as 72% following the administration of aspirin,¹⁹ thus raising the question of whether the use of aspirin is adequate as a thromboprophylaxis agent.

LOW MOLECULAR WEIGHT HEPARINS

The use of LMWH has gained enthusiasm within the orthopedic community due to its well-documented bioavailability and the absence of monitoring for clotting indices (ie, INR). The efficacy of LMWH is well documented. In multiple randomized trials, including THA and TKA patients, LMWH has been more effective than warfarin in limiting overall DVT rates. However, LMWH is associated with higher bleeding rates. Because the selection of a prophylaxis agent is a balance between efficacy and safety, some surgeons choose other modes of prophylaxis due to concerns related to bleeding and its impact on overall outcomes. An additional consideration with any medication choice is the cost; the cost of LMWH remains relatively high as compared with aspirin and warfarin.

As with any postoperative chemoprophylaxis regimen, duration of treatment is always of concern. The ACCP guidelines have changed their recommendations since the initial guidelines introduced in 1998. The most recent recommendation from the ACCP in 2008 states that patients undergoing THA or TKA should receive chemoprophylaxis with LMWH for 7 to 10 days (Grade IA recommendation), and this may be extended to up to 35 days following THA. Administration of LMWH for 35 days following TKA received a Grade 2B recommendation.¹³ As stated previously, the choice of agent as well as the duration of prophylaxis is based on a risk versus benefit analysis which should be individualized for each arthroplasty patient.

FONDAPARINUX

Fondaparinux is a newer synthetic pentasaccharide that is a potent inhibitor of Factor Xa in the clotting cascade. The typical dosing is 2.5 mg/d administered subcutaneously with the first dose being given at 6 to 12 hours postoperatively. This drug is not recommended for patients that weigh less than 50 kg or those with renal insufficiency. As with LMWH, the concern associated with the use of fondaparinux is for bleeding complications in the postoperative period.²⁰

Table 1
Levels of evidence

Level I	High-quality randomized trial
Level II	Cohort study (good control)
Level III	Case-control study
Level IV	Uncontrolled case series
Level V	Expert opinion

Table 2
Consensus recommendations from the AAOS work group

General Recommendation	Level of Evidence	Grade
Assess all patients preoperatively with regard to their risk (standard vs high) of pulmonary embolism	Level III	Grade C
Assess all patients preoperatively with regard to their risk (standard vs high) of bleeding complications	Level III	Grade C
Consider vena cava filter placement for patients who have a known contraindication to anticoagulation therapy	Level V	Grade C
Consider intraoperative or immediate postoperative mechanical compression	Level III	Grade B
Consider regional anesthesia for the procedure (in consultation with anesthesia team)	Level IV	Grade C
Consider use of mechanical prophylaxis postoperatively	Level IV	Grade C
Rapid patient mobilization	Level V	Grade C
Routine screening for thromboembolism is not recommended	Level III	Grade B
Educate the patient about symptoms of thromboembolism	Level V	Grade B

Data from Johanson NA, Lachiewicz PF, Lieberman JR, et al. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. *J Am Acad Orthop Surg* 2009;17(3):183–96.

The use of fondaparinux received a Grade 1A recommendation from the ACCP for use in patients undergoing primary elective TJA. Regarding duration of treatment, the most recent changes to the ACCP guidelines in 2008 support the use of the agent for 35 days after THA (Grade 1A) and after TKA (Grade 1B).^{13,21} There are concerns about using this drug in patients at an increased rate of bleeding as seen in the AAOS guidelines, but this is not an evidence-based recommendation.

WARFARIN

Warfarin is the oldest vitamin K antagonist used for chemoprophylaxis, with the longest track record of use in the postoperative period following primary hip or knee arthroplasty. The traditional nature of medicine has helped maintain warfarin as a popular agent, because it was the treatment of choice when most orthopedic surgeons trained during residency. Warfarin has demonstrated efficacy as an effective chemoprophylaxis agent against thromboembolic disease; however, it is not without its disadvantages. Immediately post administration, the patient is in a relatively hypercoagulable state due to diminished levels of protein C and protein S via actions of the drug. Each patient requires daily dosing and the blood is monitored daily for an INR level to determine the appropriate dose to administer. Warfarin is very sensitive to dietary changes and has interactions with several medications that may be

concomitantly taken by a patient for other comorbid conditions (Table 3). As a result, the goal INR is difficult to achieve and maintain.

A meta-analysis of all randomized controlled clinical trials reported on the overall efficacy of warfarin as a prophylactic agent following THA. Patients treated with warfarin had the lowest rate of proximal DVT as well as symptomatic PE, with a rate of 6.3% and 0.16%, respectively. The risk of major postoperative bleeding in these patients was no higher than that in patients treated with a placebo.⁴

The use of warfarin as an effective prophylactic agent following TKA has been thoroughly demonstrated over several decades.^{22–26} Additional

Table 3
Common drug interactions with warfarin

Trimethoprim-sulfamethoxazole (Bactrim)
Rifampin
Macrolide antibiotics (ie, erythromycin)
Quinolone antibiotics (ie, ciprofloxacin)
Metronidazole (Flagyl)
Certain cephalosporins (cefamandole)
Thyroid hormones (ie, levothyroxine)
Phenytoin (Dilantin)
Cimetidine (Tagamet)
Anitarrhythmics (ie, amiodarone)
Herbal medications (ie, garlic)

randomized clinical trials have compared the efficacy of warfarin with that of LMWH.^{24,26–29} In every study, LMWH was more effective than warfarin as a prophylactic agent, but there was no significant difference in the rates of symptomatic proximal DVT or PE. The postoperative bleeding rates were typically higher in the LMWH group.^{24,26,29}

With regard to the goal INR, different clinical guidelines present differing recommendations. According to the ACCP clinical guideline, a goal INR of 2.0 to 3.0 received a Grade 1A recommendation. This recommendation was made based on randomized trials that used an INR range of 2.0 to 3.0 as the target for prophylaxis.¹³ For each scenario depicted by the AAOS where the use of warfarin is warranted, the goal INR is 2.0 or less. The difference in the goal INR is based on risk versus benefit between prophylaxis against thromboembolic disease and bleeding risk. The AAOS guidelines consistently make recommendations that are more conservative and attempt to minimize the postoperative bleeding risk and hematoma formation.

As with the use of LMWH, the ACCP guidelines have changed their recommendations regarding the duration of warfarin use following primary hip or knee replacement. The 2008 ACCP guidelines recommend up to 35 days of warfarin use (goal INR 2.0–3.0) with a Grade 1B recommendation for THA and a Grade 1C recommendation for TKA patients. The AAOS recommendation, for patients of standard risk for PE and bleeding, is 2 to 6 weeks of treatment with low-dose warfarin (goal INR ≤ 2.0). Even in patients with an elevated PE and bleeding risk, low-dose warfarin is recommended for 2 to 6 weeks.

ASPIRIN

Acetylsalicylic acid (aspirin) has gained in popularity as an agent for DVT prophylaxis following total joint replacement because it is safe, inexpensive, does not require monitoring, is easy to administer, and lends itself to high patient compliance. The recommended dosing in the postoperative period is 325 mg twice daily for the duration of treatment.¹⁸ The use of aspirin is based on the premise that chemoprophylaxis should be administered to reduce the risk of PE and subsequent death, not DVT; inherent to this argument is that DVT should not be used as a surrogate for PE because all patients with a DVT do not inevitably get a PE.

Aspirin does not interfere with anesthetic administration because it does not increase the risk of neuraxial bleeding. The use of an epidural catheter for pain control requires that postoperative

chemoprophylaxis be timed appropriately to minimize the risk of epidural hematoma formation.³⁰ Aspirin functions by way of inhibiting platelet aggregation, and if given immediately preoperatively, can function in this manner intraoperatively and in the immediate postoperative period; other chemoprophylaxis agents exhibit a postoperative delay before the onset of the desired prophylaxis effect. The major benefit associated with aspirin use is its low prevalence of wound-healing problems, hematoma formation, and other serious bleeding complications that are readily associated with more potent anticoagulant agents.³¹

In the arena of TKA, aspirin has been equally as effective as other anticoagulant agents when fatal PE is used as an end point.³² Lotke and colleagues³³ reported on 2800 consecutive primary TKAs in patients treated with aspirin and mechanical prophylaxis, demonstrating a low rate of bleeding complication and a fatal PE risk of 0.1%. However, aspirin is not as effective in decreasing the risk of symptomatic DVT in the setting of THA. The Pulmonary Embolism Prevention trial was a randomized clinical trial designed to evaluate the efficacy of aspirin in preventing symptomatic VTE disease following THA. More than 4000 patients were randomized to receive aspirin ($n = 2047$) or a placebo ($n = 2041$) for 35 days following surgery. There was no statistical difference in the rate of symptomatic DVT between the 2 groups ($P > .5$).

In general, venous thromboembolic events following primary hip and knee arthroplasty has decreased significantly over the past decade, mainly due to a multidisciplinary approach. Rapid postoperative mobilization, optimization of surgical technique, and improved perioperative pain management, including the use of regional anesthesia, have all contributed to decreasing the DVT risk. The ACCP guidelines do not support the use of aspirin for prophylaxis following TJA, because this drug has not been extensively evaluated in multicenter randomized trials. The AAOS guidelines support the use of aspirin for 6 weeks except in patients that are at high risk for PE and have standard bleeding complication risk; these patients are not candidates for aspirin use because of the identified preoperative elevated risk for PE.

Because the selection of a prophylaxis agent is a balance between safety and efficacy, aspirin combined with mechanical devices is an attractive regimen for some orthopedic surgeons for their routine TJA patients. Although aspirin is less potent than other chemoprophylactic agents, it is also associated with less bleeding. Aspirin needs to be evaluated in large randomized trials that assess symptomatic events to determine its true efficacy.

MECHANICAL PROPHYLAXIS (PNEUMATIC COMPRESSION BOOTS AND INTERMITTENT PLANTAR COMPRESSION DEVICES)

The use of mechanical prophylaxis is predicated on the premise that decreasing lower extremity venous stasis in conjunction with increasing venous blood flow will decrease the likelihood of clot formation.^{34,35} Pneumatic compression boots affect local fibrinolysis, but do not affect systemic fibrinolytic activity.³⁶ Intermittent plantar compression devices were designed to replicate the hemodynamic effects of normal walking by rapid emptying of the plantar arch during the compression phase of the device.¹² The advantages of mechanical prophylaxis are evident and include an absence of monitoring and no risk of bleeding. In addition, intermittent plantar compression devices are thought to be less cumbersome than pneumatic boots, which extend the length of the entire lower leg. However, the major disadvantages are that prophylaxis ceases on patient discharge from the hospital, and patient compliance is critical to either device being effective.

Several randomized clinical trials have demonstrated that pneumatic compression boots can limit distal thrombus formation.^{23,37–41} As a result, there has been concern regarding the efficacy of mechanical compression in reducing the rates of proximal clot formation in the setting of THA. Small randomized trials have compared pneumatic compression boots and warfarin in patients undergoing THA and have demonstrated that mechanical prophylaxis is less effective than chemoprophylaxis in the prevention of proximal clot formation.^{39–41} Regarding intermittent plantar compression devices, low-powered studies have shown a decrease in overall thrombosis rates following THA.^{42–44} However, given the risk of PE from a proximal clot source, further investigation is required before mechanical prophylaxis can be recommended as a sole means of prophylaxis in patients undergoing THA.

The use of mechanical prophylaxis in the setting of TKA, both pneumatic compression and intermittent plantar compression, has been studied in several small studies.^{19,23,44–49} Although these studies were low powered, a significant reduction in thrombus formation following TKA was demonstrated. On basis of these reports, both pneumatic compression and intermittent plantar compression devices are effective in reducing clot formation following primary TKA. However, larger, multi-center randomized trials comparing mechanical and chemoprophylaxis regimens are necessary to determine the true efficacy of these devices.

AUTHORS' COMMENTARY ON CURRENT GUIDELINES

The basic difference between the ACCP and the AAOS guidelines is that the chest physicians believe that asymptomatic clots are clinically relevant. Therefore, the ACCP guidelines were developed from the data obtained from randomized trials, which used venogram data as a surrogate outcome measure. In contrast, the AAOS guidelines reflect the concerns of orthopedic surgeons with a focus on symptomatic clots, PE, and bleeding risk. Furthermore, the AAOS guidelines highlight the importance of developing prophylaxis regimens for each individual patient based on PE and bleeding risk. This is an important concept, which moves us toward risk stratification. Unfortunately, it is difficult to risk stratify most patients based on available data but it is a goal to strive for in the future.

Surgeons need to be aware that the SCIP guidelines recommend LMWH, fondaparinux, and/or warfarin for THA and TKA patients. Pneumatic compression devices are also acceptable for patients undergoing TKA procedures. Therefore, aspirin and pneumatic compression devices are acceptable for TKA patients. A surgeon may choose to use another regimen because of concerns about bleeding, but this must be documented in the medical record.

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