



Clinical Guide - VTE Prophylaxis in Major Orthopedic Surgery

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Introduction

Total hip and knee arthroplasty, and hip fracture, are associated with a high risk of deep vein thrombosis (DVT) due to the accompanying blood vessel trauma, venous stasis, coagulation activation, and older age of most patients. Before thromboprophylaxis was used routinely, DVT, which is often clinically silent, occurred in 40-60% of these patients. Pulmonary embolism occurred in 5-10%, and fatal embolism, occurring in 1-2% of patients, was the most common cause of death.

Although changes in surgical and anesthetic techniques, and earlier mobilization, may have reduced the risk of venous thromboembolism somewhat, routine thromboprophylaxis remains extremely important and is standard of care. Effective prophylaxis has been shown to reduce the rate of DVT by at least 50%.

Thromboprophylaxis for Hip or Knee Arthroplasty

The following methods of thromboprophylaxis have proven to be effective for total hip or knee arthroplasty:

- a. A low molecular weight heparin (LMWH); once or twice daily SC dosing.
- b. The pentasaccharide, fondaparinux; once daily SC dosing.
- c. Direct thrombin inhibitor, dabigatran etexilate; once daily oral dosing.
- d. Direct Xa inhibitor, rivaroxaban; once daily oral dosing.
- e. Warfarin in doses to prolong the INR to 2.0 - 3.0.

The following options are NOT recommended as sole methods of prophylaxis after major orthopedic surgery: low dose heparin, aspirin, graduated compression stockings, intermittent pneumatic compression (IPC) devices. IPC devices and venous foot pumps appear to provide some protection, but the evidence is limited, they are probably less effective than the anticoagulant alternatives, and are cumbersome, often disliked by patients, and cannot be used after discharge. IPC devices should be confined to patients with valid absolute contraindications to anticoagulants, and should be replaced with anticoagulant prophylaxis when the contraindication resolves.

Practice Points for Hip and Knee Arthroplasty Thromboprophylaxis

- Meta-analyses have shown a consistent correlation between the prevention of venographic DVT and the prevention of symptomatic DVT.
- For both hip and knee arthroplasty, when venography was used as the end-point in comparative clinical trials, LMWHs were shown to be superior to warfarin.
- Using a venography endpoint, fondaparinux, started 4-8 hours after surgery, was superior to the LMWH, enoxaparin, started the day after surgery. At least some of the improved efficacy with fondaparinux over LMWH may be a result of its earlier initiation.
- Studies using venographic endpoints suggest that dabigatran is equivalent to LMWH (enoxaparin) when the latter is used at a dose of 40 mg once daily, begun preoperatively, and inferior to LMWH (enoxaparin) used at a dose of 30 mg BID, begun post-operatively.
- Studies using venographic endpoints as primary outcomes, and clinical events as secondary outcomes, suggest that rivaroxaban is superior to LMWH (enoxaparin) administered either once or twice daily.
- Two studies directly compared two different LMWH preparations used at approximately equivalent doses and showed no difference in asymptomatic DVT in either.
- Studies using symptomatic thromboembolic endpoints (without screening for asymptomatic DVT) demonstrate that LMWH and warfarin provide similar protection following hip or knee arthroplasty.
- Clinically important postoperative bleeding complications are uncommon with warfarin, low molecular weight heparin, dabigatran etexilate and rivaroxaban. Fondaparinux appears to have a slightly higher rate of bleeding (increase of 1%) that is

not observed if the initial dose is administered more than 6 hours postoperatively.

- Prophylaxis studies have generally excluded patients with prior DVT and those at high risk of bleeding; therefore, much less is known about the effectiveness and safety of any prophylaxis modality in these patient groups.
- Pre-discharge screening tests for asymptomatic deep vein thrombosis (eg. ultrasound or venography) are not recommended.

Duration of Prophylaxis after Major Orthopedic Surgery

- Prophylaxis should be continued for at least 10 days. Although studies in which at least 7 days of prophylaxis was used show a substantial number of asymptomatic thrombi on venography after hospital discharge, studies using clinically important endpoints indicate that few symptomatic thromboembolic events occur if prophylaxis is continued for at least 10 days.
- Many randomized trials demonstrate that in-hospital LMWH prophylaxis for approximately 7 days is associated with at least twice as many asymptomatic DVTs, using routine screening venography, as prophylaxis continued for up to 35 days (extended prophylaxis). Meta-analyses have also demonstrated a significant reduction in symptomatic thromboembolic events with extended prophylaxis in hip arthroplasty patients. One randomized trial comparing extended prophylaxis with rivaroxaban (for approximately 35 days) to shorter prophylaxis (10-14 days) with enoxaparin showed that both asymptomatic DVT and symptomatic thromboembolic events were reduced with extended prophylaxis in hip arthroplasty patients. In knee arthroplasty studies, the reduction in both asymptomatic and symptomatic thromboembolic events with prolonged thromboprophylaxis was of lesser magnitude and not significant.
- At least one study has shown potential benefit with warfarin prophylaxis given for a similar duration as LMWH following hip arthroplasty, although another randomized trial found that patients who received oral anticoagulant prophylaxis after discharge from hospital experienced more bleeding than those who received LMWH.
- Therefore, although the optimal duration of post-discharge prophylaxis is not known, most experts now advise continued prophylaxis for a minimum of 10 days and up to 35 days (particularly after hip arthroplasty).

Low Molecular Weight Heparins and Fondaparinux

Dalteparin, enoxaparin, nadroparin, tinzaparin, and fondaparinux have been approved for the prevention of DVT following total hip and/or knee arthroplasty. (The approved indications, precautions and dosing for each agent may be found in the CPS.)

- LMWHs are commonly commenced postoperatively and usually not until the morning following surgery. Initiation of LMWH with half the usual dosage 4 hours or more postoperatively is efficacious after hip arthroplasty without increased bleeding. This regimen showed a significant reduction in asymptomatic distal and proximal DVT compared with warfarin.
- Fondaparinux is commenced at least 6 hours after surgery.
- Although heparin-induced thrombocytopenia (HIT) is less common with LMWHs than with unfractionated heparin, LMWH should be avoided in patients with a prior history of HIT.
- Perispinal hematoma is a rare but serious complication of spinal or epidural anesthesia and epidural analgesia. For patients receiving ongoing epidural analgesia, antithrombotic agents should be used cautiously. If spinal or epidural anesthesia or epidural analgesia is to be used concurrently with prophylactic doses of a LMWH, it is recommended:
 1. That introduction of the catheter or needle occurs before the patient receives any LMWH;
 2. That the catheter be removed at the nadir of the LMWH anticoagulant effect (just before a dose or at least 10 hours after a BID LMWH dose or at least 20 hours after a once daily LMWH dose);
 3. That any subsequent LMWH dose be given 2 hours or more after catheter removal; and
 4. Extreme caution or avoidance of LMWH and other antithrombotic agents is recommended shortly after patients have had a traumatic epidural or spinal intervention.
- Fondaparinux presumptively also carries risks of perispinal hematoma. Given its longer half-life, fondaparinux should not be used in patients with an indwelling epidural catheter.

Warfarin Prophylaxis

- Give first dose of 5-7.5 mg on the night of surgery (depending on the patient's age and size).
- Elderly patients may be very sensitive to warfarin. Lower initial doses should be considered.
- Warfarin dose should be adjusted to achieve and maintain an INR of 2.0 - 3.0, preferably within four days.
- If an epidural catheter is used along with warfarin, the catheter should be removed while the INR is < 1.3.

Direct Oral Thombin and Xa Inhibitors

Dabigatran etexilate and rivaroxaban have been approved for the prevention of DVT following total hip and/or total knee arthroplasty

- Rivaroxaban 10 mg PO is initiated 6 to 8 hours after surgery followed by 10 mg PO daily.
- Dabigatran etexilate 100 mg or 75 mg PO is commenced 1 to 4 hours after surgery followed by 220 mg or 150 mg PO daily
 - Dabigatran etexilate 150 mg PO daily should be considered for patients with moderate renal dysfunction (CrCl 30-50 cc/min) and/or in patients older than 75 years old.
- Both rivaroxaban and dabigatran should be used for a minimum of 10 days after knee or hip arthroplasty – extension to 28 to 35 days should be considered after hip arthroplasty
- Rivaroxaban and dabigatran etexilate should not be used within 2 hours of the removal of an epidural catheter and they should not be used in patients with indwelling catheters

Thromboprophylaxis for Hip Fracture

The risk of venous thromboembolism following hip fracture is also very high.

- Thromboprophylaxis recommendations related to hip and knee arthroplasty generally apply to hip fracture as well.
- If surgery is to be delayed, preoperative prophylaxis during this delay is recommended. Unfractionated heparin or LMWH should be used in this setting as the timing of the operation may be difficult to predict.
 - a) heparin 5,000 units SC BID – no need to hold preop (unless regional anesthesia will be used);
 - b) LMWH in ½ the usual dose can be given at bedtime – no need to hold preop if surgery the next day.
- Recommended thromboprophylaxis options for hip fracture patients include: fondaparinux, low molecular weight heparin, low dose heparin, and adjusted dose warfarin (INR 2.0-3.0).
- Rivaroxaban and dabigatran should NOT be used in hip fracture patients until studies are conducted to assess their efficacy and safety in this patient group.
- There are few randomized trials of prophylaxis in hip fracture patients. A large trial, comparing the LMWH, enoxaparin, with fondaparinux demonstrated 79% fewer proximal and 55% fewer distal DVTs with fondaparinux. As in the elective hip and knee arthroplasty studies, in this trial, the fondaparinux was started earlier (4-8 hours postop) than the LMWH (12-24 hours postop).
- Fondaparinux continued for 28 days after hip fracture virtually eliminates both venographically demonstrated thrombosis and symptomatic thrombosis. By inference, LMWH and warfarin for a similar period are assumed to be of benefit.
- Prophylaxis is recommended for a minimum of 10 days and until improved mobilization (if this is likely to occur). Most experts now recommend extended prophylaxis for up to 35 days after hip fracture surgery.

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