

## Rapid Literature Review

### Chemical thromboprophylaxis after hip fracture surgery

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### Background

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Few studies are available in the literature reporting on the prevention of venous thromboembolism in patients with a hip fracture compared to those with hip arthroplasty [2].

The Director of Orthopaedic Surgery requested a review of the evidence around the most suitable chemical thromboprophylaxis for patients who have undergone hip surgery.

### Objectives

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To determine the recommended chemical thromboprophylaxis (choice, dose and duration) for patients after hip fracture surgery in the prevention of venous thromboembolism (VTE); and improvement outcomes related to deep vein thrombosis (DVT), pulmonary embolism (PE), bleeding, and mortality.

### Results

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Five sources of evidence met the inclusion criteria (Appendix 1) and were included in this review:

- Two literature reviews focusing on currently acceptable protocols of thromboprophylaxis in hip fracture patients, based on evidence from large-scale studies and existing guidelines [1, 2];
- A systematic review of randomised controlled trials and large nonrandomised comparative studies [3];
- Two randomised controlled trials investigating the impact of rivaroxaban and hemocoagulase on the prevention of VTE [4] and the reduction of bleeding [5] in hip fracture patients, respectively. Appraisal of these was not performed.

The comparative efficacy of various thromboprophylaxis components on venous thromboembolism outcomes, major bleeding, and other adverse events has been reported here, however, it is important to note that evidence is sparse in the area of VTE thromboprophylaxis after hip fracture surgery. [3] Despite the paucity of evidence, guidelines from the UK, Canada and Scotland are in agreement on the recommended acceptable post-surgery protocols and their duration [1, 2].

#### Suitable chemical thromboprophylaxis for patients after hip fracture

Common prophylactic drugs for VTE include anti-platelet agents (aspirin), unfractionated heparin (UFH), low molecular weight heparin (enoxaparin, dalteparin), vitamin K antagonists (warfarin) and factor Xa inhibitors (darexaban, edoxaban, eribaxaban, fondaparinux, rivaroxaban) [2, 3].

#### *Comparison between classes of thromboprophylaxis*

There was moderate quality of evidence (from three RCT's) to suggest a lower risk of DVT was associated with low molecular weight heparin (LMWH) as compared with factor Xa inhibitors [3]. There is insufficient evidence to evaluate outcomes of PE and bleeding; and mortality was not an evaluated outcome of interest [3].

#### *Comparison within a class of thromboprophylaxis*

There was insufficient evidence evaluating within class intervention comparisons (i.e., LMWH: Enoxaparin vs Dalteparin or Semuloparin) [3].

#### *Comparison between single or combined interventions*

No studies compared single class and combination class interventions after hip fracture surgery [3].

Network meta-analysis suggests that comparisons between specific pairs of classes or interventions were too sparse to yield sufficient conclusions regarding risks of total DVT or major bleeding. Although there were no statistical differences between classes, factor Xa inhibitors and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions [3].

Fondaparinux is the most commonly used factor Xa inhibitor and suggested as a primary option by the NICE and SIGN for prevention of postoperative VTE after hip fractures [2].

New oral anticoagulants such as dabigatran, rivaroxaban and apaxiban are well studied and recently proposed and prescribed for prevention and treatment of thrombosis in total knee and hip arthroplasty [1]. However, strong evidence to support their use in patients with fractures around the hip is lacking, and further studies are required in order to establish their routine use in hip fracture surgery [1].

In a double-blinded RCT (n = 287 patients with hip fracture), Tang (2017) reported a lower incidence of VTE in the Rivaroxaban group as compared to that in the LMWH (Enoxaparin) and sequential therapy (Enoxaparin + Rivaroxaban) groups (R:5.21%; LMWH: 14.74%, and ST: 10.42%; p<0.091) [4]. However, the incidence of VTE and other outcomes such as bleeding, mortality, PE, and DVT were not significantly different among the three groups under a 28-day administration regime [4].

### **Chemical thromboprophylaxis dose and duration**

Data was insufficient to summarise the evidence for different dose or duration of interventions for hip fracture surgery. None of the studies of hip fracture surgery compared different intervention doses or regimens [3].

Nevertheless, established guidelines exist in the UK and Canada [1, 2]. Table 1 summarises guideline recommendations that include the duration of the choice chemical thromboprophylaxis, as presented in two recent reviews [1, 2].

In general the findings indicated:

- The time to initiation of postoperative pharmacological prevention varies from the 6 to 12 hours after surgery and,
- The duration recommended by clinical practice guidelines vary between 28 to 35 days.

The exact duration of prevention are likely to be informed by the presence of underlying conditions, intraoperative findings, postoperative status of the wound and others [2].

### **Other choices of chemical thromboprophylaxis being studied**

In a single-blinded RCT (n = 100 patients), intravenous *hemocoagulase agkistrodon* (an enzyme present in snake venom) was shown to significantly reduce blood loss in geriatric patients undergoing cementless hemiarthroplasty compared to its saline control group (225.16 ± 67.74 ml vs. 277.95 ± 96.05 ml, P < 0.01).

No cases of severe complications or short-term adverse events including DVT or PE were reported [5].

**Table 1.** Guideline recommendations of the choice, timing and duration of chemical thromboprophylaxis [1, 2]

Source of recommendations	Year	Choice of chemical thromboprophylaxis	Timing post-surgery	Duration
The National Hip Fracture Database National Report [6]	2010	Heparin (UFH <sup>^</sup> or LMWH)	6-12 hours	28 to 35 days
		Fondaparinux	6 hours	28 to 35 days
<i>Management of hip fracture in older people: a national clinical guideline.</i> Scottish Intercollegiate Guidelines Network (SIGN) [7]	2009	Heparin (UFH <sup>^</sup> or LMWH)	6-12 hours	28 days
		Fondaparinux	6 hours	28 days
		Aspirin is NOT recommended post-operatively as monotherapy for hip fracture		
<i>Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.</i> National Collaborating Centre for Acute and Chronic Conditions (NCC-ACC) / National Institute for Health and Care Excellence (NICE) [8]	2015	Heparin (UFH <sup>^</sup> or LMWH)	6-12 hours	28 to 35 days
		Fondaparinux sodium	6 hours #	28 to 35 days
<i>The care of patients with fragility fracture.</i> British Orthopaedic Association (BOA) [9]	2007	Fondaparinux or LWMH and the simultaneous use of mechanical VTE prophylaxis	6-12 hours	4 weeks
<i>Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.</i> American College of Chest Physicians (ACCP) [10]	2012	Heparin (LMWH)	Not mentioned	35 days
		Fondaparinux	6-8 hours	35 days
		Warfarin (target INR 2.5)	Not mentioned	35 days
<i>Thromboprophylaxis: orthopedic surgery.</i> Thrombosis Interest Group of Canada (TIGC) [11]	2016	Fondaparinux	12 hours	14 to 35 days
		Warfarin	Not mentioned	14 to 35 days

**Key:**  
LMWH – Low molecular weight heparin  
UFH – Unfractionated heparin  
VTE – venous thromboembolism  
TIGC – Thrombosis Interest Group of Canada

INR – international normalized ratio;  
# – after surgical closure, provided haemostasis has been established and there is no risk of bleeding;  
^ – for patients with renal failure

## Discussion

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The comparative efficacy of various thromboprophylaxis components on venous thromboembolism outcomes, major bleeding, and other adverse events reported in the 2017 systematic review was based on only 12 eligible studies. The authors conclude that evidence is sparse in the area of VTE thromboprophylaxis after hip fracture surgery.<sup>[3]</sup>

Subcutaneous administration of heparin causes a certain degree of trauma to patients and is inconvenient in routine practice<sup>[4]</sup>. Therefore, sequential therapy (combining LMWH and Rivaroxaban) is being studied and has shown to increase compliance<sup>[4]</sup>. Sequential therapy increased patient compliance by reducing the inconvenience caused by the subcutaneous injection (of LMWH), and reducing high treatment cost (when using Rivaroxaban alone)<sup>[4]</sup>. These results were based on only one RCT, and must be interpreted with caution.

Aspirin is taken regularly by 30% of patients presenting with hip fracture, therefore Scottish guidelines caution of the risk of significant bleeding if aspirin is taken in combination with other thromboprophylactic medication<sup>[1]</sup>. Furthermore, these guidelines recommend against using aspirin post-operatively as monotherapy for hip fracture.<sup>[1]</sup>

Although evidence around thromboprophylaxis in post-surgical hip fracture patients is sparse, guidelines from the UK, Canada and Scotland are in agreement on the recommended acceptable post-surgery protocols and their duration<sup>[1, 2]</sup>.

## Conclusions

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Prevention of postoperative VTE may be initiated with the same methods applied to patients undergoing ordinary hip surgery<sup>[2]</sup>.

Based on moderate strength of evidence, LMWH results in lower risk of total DVT than Factor Xa inhibitor<sup>[3]</sup>. For other intervention comparisons, there is insufficient evidence available to assess the effect of choice of thromboprophylaxis on other outcomes such as PE, bleeding or mortality<sup>[3]</sup>.

New oral anticoagulants such as dabigatran, rivaroxaban and apixaban are recently proposed and prescribed for prevention and treatment of thrombosis in total knee and hip arthroplasty, but strong evidence does not exist with regard to their use in patients with fractures around the hip<sup>[1, 2]</sup>. Therefore, additional studies are required to assess their efficacy for VTE prophylaxis after hip fracture<sup>[2]</sup> in order to establish their routine use in hip fracture surgery<sup>[1]</sup>.

There is insufficient evidence to summarise different dose or duration of interventions for hip fracture surgery<sup>[3]</sup>. Collectively, several distinguished guideline sources in the UK, Scotland and Canada recommend restarting patients on heparin (UFH or LMWH) and Fondaparinux 6-12 hours post-surgery for a duration of 28 to 35 days<sup>[1, 2]</sup>. The UK and Scottish guideline protocols further recommend stopping UFH or LMWH 12 hours prior to surgery and then continuing as prescribed above, with the exception of Fondaparinux sodium, which should be stopped 24 hours prior to surgery; and using UFH for patients with renal failure<sup>[1]</sup>.

## References

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## Appendix 1

### Search strategy

#### Inclusion/Exclusion Criteria

**Table 2.** Inclusion/Exclusion criteria

<b>Population</b>	<b>Include:</b> Hip fracture, hemiarthroplasty patients, proximal femoral fracture <b>Exclude:</b> Hip arthroplasty, total hip replacement
<b>Interventions</b>	<b>Include:</b> Post-surgical thromboprophylaxis (chemical or combination); include dose and duration of treatment <b>Exclude:</b> Mechanical thromboprophylaxis
<b>Outcomes</b>	<b>Include:</b> Deep vein thrombosis (DVT), pulmonary embolism (PE), bleeding outcomes, mortality rate
<b>Context</b>	<b>Include:</b> Adult <b>Exclude:</b> Paediatric
<b>Types of evidence</b>	<b>Include:</b> Systematic reviews, meta analyses, RCT
<b>Limits</b>	<b>Date:</b> 2015 to current <b>Language:</b> Publications in English.

**Table 3.** The following databases and search strategies were followed

Database	Search terms	Filters
Pubmed	Thromboprophylaxis or 'anticoagulation therapy' or prophylaxis AND femur OR hip OR 'proximal hip' OR 'proximal femur' AND fracture	Filter for humans, reviews & RCTs, and from 2015.
Ovid EMBASE	Thromboprophylaxis or 'anticoagulation therapy' or prophylaxis AND femur OR hip OR 'proximal hip' OR 'proximal femur' AND fracture	Filter for humans, reviews & RCTs, and from 2015.
TRIP	Hip fracture AND thromboprophylaxis	Nil
Cochrane library	Thromboprophylaxis or 'anticoagulation therapy' or prophylaxis AND femur OR hip OR 'proximal hip' OR 'proximal femur' AND fracture	Nil
NICE	Hip, fracture, prophylaxis	Nil

## Study Selection

Titles and abstracts identified were screened using inclusion and exclusion criteria established *a priori*. Searches of each database were screened by one reviewer in consultation with colleagues as necessary. Literature was included based on the above criteria (Table 1).

