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Interventions for the primary prevention of venous thromboembolism for hip fracture surgery (Protocol)

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[Intervention Protocol]

Interventions for the primary prevention of venous thromboembolism for hip fracture surgery

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of pharmacological or mechanical interventions, or both combined, for the primary prevention of venous thromboembolism in individuals undergoing hip fracture surgery.

BACKGROUND

Description of the condition

Venous thromboembolism (VTE) describes the abnormal formation of thrombus in the veins, commonly in the deep venous system of lower limbs (deep vein thrombosis, or DVT), or the subsequent embolisation to the pulmonary circulation (pulmonary embolisation, or PE). DVT presents as unilateral leg pain and swelling or may be detected following diagnosis of PE. Left undiagnosed and untreated, DVT may later progress into post-thrombotic syndrome (PTS) (persistent swelling, erythema, and ulceration). PE presents acutely, with shortness of breath, pain on inspiration, tachycardia, and right heart overload. If left untreated, it can lead to circulatory collapse and death. In survivors of PE, it can also cause chronic thromboembolic pulmonary hypertension (CTEPH) in the longer term. Venous thromboembolism also includes (intraoperative) fat-embolisation (both as a result to trauma but also fat extravasation during open reduction internal fixation) with secondary appositional thrombus formation (Rothberg 2019). Increasingly, in the era of more liberal central venous catheterisation, DVT may involve the upper extremities. Rarely, other venous circulation (such as cerebral veins, portal and mesenteric veins, etc.) can also be affected (Streiff 2016).

In addition to DVT and PE, a thrombus can also form in the superficial veins, where it is associated with local pain and inflammation and reduced mobility (superficial venous thrombosis). This tends to be associated with lower mortality and morbidity rates than DVT, although some patients may be at a higher risk of DVT formation depending on the location of the clot (Chengelis 1996; Nasr 2005).

VTE can occur spontaneously and is broadly classified as provoked or unprovoked (Kearon 2016). VTEs which have no underlying or immediately apparent cause are referred to as unprovoked. VTE with possible causes such as long periods of inactivity, dehydration, hospitalisation, trauma, clotting disorders and previous thrombosis, varicose veins with phlebitis, pregnancy, oral combined hormonal contraceptive use, malignancy, obesity, smoking, and age are described as provoked VTE (Anderson 2003; NICE 2019).

The incidence of VTE in mostly Caucasian populations (understood to be white populations) is between 100 and 200 per 100,000 person-years (Heit 2015; White 2003). Of these, it is estimated that 45 to 117 per 100,000 person-years are due to DVT (without PE), and 29 to 78 per 100,000 person-years are due to PE (with or without DVT) (Heit 2015). Recurrent VTE occurs in approximately 7.4% of patients at one year, rising to 30.4% of patients by 10 years (Cushman 2007; Heit 2015; White 2003). A recent review found that in individuals with unprovoked VTE, the risk of recurrent VTE after discontinuing anticoagulation was 10% in the first year, rising to 36% at 10 years, with 4% of recurrent VTE events resulting in death (Khan 2019). The prevalence of DVT in individuals with superficial vein thrombosis (SVT) is 18.1%, and PE prevalence is 6.9% (Di Minno 2016). The incidence of CTEPH after PE is 0.56% for all patients and 3.2% in survivors of PE (Ende-Verhaar 2017).

In patients with clinical signs and symptoms that are suggestive of venous thrombosis, diagnostic algorithms usually include calculating a clinical probability score (Bates 2012; NICE 2012). The predicted risk can then be used in combination with D-dimer testing or imaging (including ultrasound and computerised tomography pulmonary angiogram (CTPA)), or both, to confirm a diagnosis of VTE.

Hip fractures are the most common fracture in adults aged over 60 years, and patients suffering neck of femur fractures pose a large burden to healthcare systems around the world. In the UK alone, approximately 66,000 hip fractures are registered annually. Hip fractures are classified as ‘fragility’ fractures, with the term often representing the patient as a whole. These patients are complex with multiple comorbidities (NICE 2019). Over 50% of neck of femur fractures are graded by the American Society of Anesthesiologists as grade 3, meaning "a patient with severe systemic disease". This unfortunately results in an overall average mortality rate of 6% at 30 days, and 33% at one year (RCP 2019). In the UK, National Institute for Health and Care Excellence (NICE) guidelines therefore advise that these patients be treated via a multidisciplinary team-based approach. The goals are for patients to receive their surgery on the day of diagnosis or the day after, with immediate weight-bearing and mobilisation on the first postoperative day (RCP 2019). The careful balancing of surgery and anticoagulation play an integral role in the care for these patients (NICE 2019; NICE 2020).

Adults who experience hip fracture trauma are more likely to have certain risk factors commonly associated with VTE, including periods of inactivity, hospitalisation, trauma, and older age. VTE is a relatively common and potentially fatal complication following hip fracture surgery (Shin 2017).

Description of the intervention

Prophylactic strategies in those at risk (e.g. those undergoing surgical procedures for hip fracture) are recommended by national and international guidelines, such as those published by NICE in the UK (NICE 2019; NICE 2020), the American College of Chest Physicians in the USA (Guyatt 2012; Kahn 2014), European guidelines from the European Society of Cardiology and the ESA VTE Guidelines Task Force (Afshari 2018; Mazzolai 2018), and a guideline on behalf of the Thrombosis and Haemostasis Society of Australia and New Zealand (Tran 2019). Prophylactic strategies include the use of both mechanical methods and pharmacological methods, including direct oral anticoagulants (DOACS) as well as parenteral anticoagulation (Alikhan 2014; Kakkos 2016; McCormack 2020; Sachdeva 2018).

There are various different pharmacological and mechanical interventions available for the primary prevention of VTE, including:

- pharmacological methods, which may include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), direct thrombin inhibitors, factor Xa inhibitors, and antiplatelets;
- mechanical methods, which may include mobilisation techniques, antiembolism stockings, intermittent pneumatic compression devices (IPC) devices, foot pumps or foot impulse devices, electrical stimulation, and continuous passive motion.

How the intervention might work

Pharmacological prophylaxis is required immediately after the hip fracture trauma, taking into account the need for surgery at the soonest possible time. The time to half-life and the

onset of action are therefore crucial to decision-making between the different pharmacological agents. A person's individual risk of VTE needs to be weighed against their risk of bleeding from pharmacological thromboprophylaxis. Some drugs require injection and some are prescribed orally. Pharmacological methods help to prevent the formation of blood clots and therefore thromboembolic complications. Antithrombotic agents interrupt coagulation pathways (Ageno 2010); they mainly act either by inhibiting platelet function directly or inhibiting platelet activation and fibrin formation via thrombin inhibition. For example, heparin exerts anticoagulant activity by activating antithrombin, which accelerates the inactivation of coagulation enzymes; vitamin K helps to make various proteins that are needed for blood clotting and regulates the process of blood coagulation; antiplatelets stop platelets forming a clot; direct thrombin inhibitors directly inhibit thrombin to delay clotting; and factor Xa inhibitors block the activity of clotting factor Xa, preventing clot formation. Mechanical prophylaxis aims to prevent venous congestion through pressure to help blood flow. Compliance may vary between these different types of interventions, which will impact on the effectiveness of the intervention (Flevas 2018).

Why it is important to do this review

There are various different pharmacological and mechanical interventions available for VTE prophylaxis, and there is a need to review the body of evidence for older adults who experience hip fracture trauma and require surgery. There are Cochrane Reviews of various interventions for VTE following elective hip surgery (compression, other anticoagulants, transfusion, neuromuscular electrical stimulation, pentasaccharides) (Forster 2016; Hajibandeh 2017; Salazar 2010; Zhao 2014). There are relatively fewer studies on the prevention of VTE in hip fracture patients compared with elective hip surgery patients (Shin 2017). This may be because adults who experience hip fracture trauma represent a different patient population, that is older adults, who are most likely frail with multiple comorbidities, and who may respond differently to prophylactic treatment (Handoll 2002; NICE 2020).

There is one Cochrane Review that partially covers this topic for the patient population of interest (Handoll 2002). This includes only injectable anticoagulants (UFH or LMWH), and physical agents such as compression stockings and arteriovenous foot pumps. We intend that this review will replace Handoll 2002 with a broader scope and up-to-date evidence, including all types of pharmacological and mechanical interventions available for the primary prevention of VTE.

Outside of Cochrane, a NICE guideline (NG89) published in 2018 and updated in 2019 recommends prophylaxis for people with fragility fractures of the pelvis, hip or proximal femur from a National Health Service (NHS) hospital-based perspective (NICE 2019). The NICE guideline is underpinned by evidence published and added to the searched databases up until June 2017. The NICE guideline recommends LMWH or fondaparinux sodium (factor Xa inhibitor) for postoperative prevention of VTE after frailty fractures of the hip provided the risk of VTE outweighs the risk of bleeding; and IPC at time of admission if pharmacological prophylaxis is contraindicated. It is anticipated that our review will identify studies published since this date, as well as identify studies excluded from the NICE review because they were in abstract form, unpublished, or in a foreign language. A potentially important contextual aspect is that in many (but not all) countries, early mobilisation (and perhaps early surgery) are likely to have changed over time and influenced the risk of VTE.

There is a clear need to answer the clinical question: What is the best prophylaxis intervention for venous thromboembolism for patients undergoing hip fracture surgery? To answer this question it is important to review the evidence for all interventions (pharmacological and mechanical) available for the primary prevention of VTE in adults who experience a hip fracture and require hip fracture surgery. This review is likely to benefit orthopaedic and vascular surgeons, geriatric and general medical teams, nursing staff, physiotherapists, rehabilitation specialists, and others who care for and manage patients who have undergone hip fracture surgery, as it will inform their practice. By influencing decision-making and effective care, this review is likely to benefit the patient population. It may also benefit policymakers by identifying clinically effective interventions and directing future guidelines for the care of these patients.

OBJECTIVES

To assess the effects of pharmacological or mechanical interventions, or both combined, for the primary prevention of venous thromboembolism in individuals undergoing hip fracture surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and quasi-RCTs that investigate pharmacological or mechanical interventions for the primary prevention of VTE in individuals undergoing hip fracture surgery. Parallel (e.g. cluster or individual) designs will be eligible for inclusion; studies with a cross-over design will be excluded. We will include studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We will include male and female adults aged > 60 years with proximal femoral fracture (hip fracture) having non-elective surgery for their hip fracture. We will include any type of non-elective surgery for any type of hip fracture. We will exclude participants undergoing elective hip surgery.

We will exclude studies investigating the secondary prevention of VTE. We will exclude participants who present with DVT at baseline, participants receiving treatment for current VTE episodes, and those treated for VTE within the previous 30 days. We will exclude high-energy fractures in young adults and proximal fractures in children. We will exclude hip fractures caused by malignancy.

We will include studies involving participants undergoing other types of surgery and elective hip fracture surgery provided data are reported separately for participants aged > 60 years undergoing non-elective hip fracture surgery.

There will be no restrictions on gender, race, or educational status, care setting (hospital, community, care home), or country.

Types of interventions

We will include studies that compare any pharmacological or mechanical intervention or combination treatments versus another pharmacological or mechanical intervention or combination treatments, or no treatment (placebo, no intervention, or standard care).

Pharmacological methods may include, but are not limited to, unfractionated heparin (UFH); low molecular weight heparin (LMWH) (e.g. dalteparin sodium, enoxaparin sodium, tinzaparin sodium); vitamin K antagonists (VKA) (e.g. warfarin, acenocoumarol, phenindione); direct thrombin inhibitors (e.g. dabigatran etexilate, argatroban monohydrate, bivalirudin); factor Xa inhibitors (e.g. apixaban, edoxaban, fondaparinux sodium, rivaroxaban); and antiplatelets (e.g. aspirin).

Mechanical methods may include, but are not limited to, mobilisation techniques, antiembolism stockings, IPC devices, foot pumps or foot impulse devices, electrical stimulation, and continuous passive motion.

We will include comparisons involving the use of other agents or methods in conjunction with these interventions provided these agents or methods were applied to all groups in the study. We will include studies with more than two groups if data are available for pharmacological or mechanical intervention or combination treatments versus another pharmacological or mechanical intervention or combination treatments, or no treatment.

There will be no limits on setting, frequency, duration, or intensity of intervention. We will exclude trials with a duration of follow-up of less than seven days, or that only report data for over 150 days.

Types of outcome measures

We will include eligible trials regardless of whether they report one or more of the outcomes listed below. Relevant trials that measured these outcomes but did not report the data at all, or did not report them in a useable format, will be included in the review and described narratively.

Primary outcomes

- Venous thromboembolism (VTE): deep vein thrombosis (DVT) or pulmonary embolism (PE), symptomatic or asymptomatic, first episode, fatal or non-fatal, between the period immediately after hip fracture surgery to 90 days from hospital discharge. Diagnosis must be confirmed by clinical examination and at least one additional objective diagnostic test. Ultrasonography or angiography (e.g. by computed tomography pulmonary angiogram (CTPA), magnetic resonance imaging (MRI) or by digital subtraction) will be accepted for DVT diagnosis from any site (e.g. lower limbs, abdominal). We will accept angiography by any described method and ventilation-perfusion scan for confirmation of PE. We will also consider postmortem examination as an objective confirmation of DVT and PE. If the participant has both DVT and PE events, we will count this as one unique event of VTE for the analysis of this outcome.
- Major bleeding: a bleeding event that occurs between the period immediately after hip fracture surgery to 45 days from hospital discharge and results in death; or occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); or results in the need for a transfusion of at least two units of blood; or leads to a drop in haemoglobin of ≥ 2 g/dL; or is a serious or life-threatening clinical event.

Secondary outcomes

- All-cause mortality: reported within 90 days from surgery (or from hospital discharge if surgery date not reported).
- PE: major or minor according to Pulmonary Embolism Severity Index, symptomatic or asymptomatic, first episode, fatal or non-fatal, reported between the period immediately after hip fracture surgery to 90 days from hospital discharge. Diagnosis must be confirmed by angiography (e.g. by CTPA, MRI or digital subtraction) and ventilation-perfusion scan, or both.
- DVT: distal or proximal, symptomatic or asymptomatic, first episode, fatal or non-fatal, reported between the period immediately after hip fracture surgery to 90 days from hospital discharge. Diagnosis must be confirmed by ultrasonography or angiography (e.g. CTPA, MRI or digital subtraction).
- Infection: wound infection or peri-prosthetic joint infection (PPJI), or need for re-intervention as a result of infection, reported during study follow-up.
- Clinically relevant non-major bleeding: bleeding that does not meet the criteria for major bleed but requires medical attention or a change in antithrombotic therapy, or both, reported up to 45 days from hospital discharge.
- Health-related quality of life: measured between the period immediately after hip fracture surgery to 90 days from hospital discharge using a validated scoring system/measurement tool.
- VTE mortality: includes fatal PE, reported within 90 days from surgery (or from hospital discharge if surgery date not reported).
- Adverse events: including long-term chronic thromboembolic pulmonary hypertension, post-thrombotic syndrome affecting the leg, osteomyelitis, heparin-induced thrombocytopenia, technical complications of mechanical interventions, other adverse events (including infection and systemic complications) reported during study follow-up.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist aims to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

The Information Specialist will search the following databases for relevant trials:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 onwards);
- Embase Ovid (from 1974 onwards);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) (from 1982 onwards).

The Information Specialist has devised a draft search strategy for RCTs for MEDLINE which is displayed in Appendix 1, which will be used as the basis for search strategies for the other databases listed.

The Information Specialist will search the following trials registries:

- the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch);
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We will search the bibliographies of the included studies to identify any additional relevant articles.

Data collection and analysis

Selection of studies

We will merge the search results to remove duplicated records and then examine titles and abstracts to select relevant reports using Covidence (Covidence). We will use the methods described in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Two of the four review authors (TB, DP, SEY, BG) will independently perform title and abstract screening to identify potentially eligible articles. We will then retrieve the full-text articles for all potentially relevant titles for duplicate full-text review. Two of the four review authors (TB, DP, SEY, BG) will independently screen the full texts and identify studies for inclusion in the review. Any disagreements at each stage of the screening process will be resolved by discussion within the review team (TB, DP, SEY, BG) until consensus is reached. We will illustrate the study selection process in a PRISMA flow diagram (Liberati 2009). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table along with the reasons for their exclusion.

Data extraction and management

Two of the four review authors (TB, BG, DP, SEY) will independently extract study data using a standard data extraction form according to the methods described in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We will extract data on:

- methods (study design, number of participants, exclusions post randomisation, losses to follow-up, intention-to-treat analysis, duration of study);
- participant characteristics (e.g. country, setting, age, sex, inclusion and exclusion criteria, comorbidities, details of hip fracture surgery);
- interventions (e.g. type, dose/intensity, duration);
- comparisons;
- outcomes;
- study funding source and declaration of interest of the study authors.

We will enter data into Review Manager 5 (Review Manager 2020) or RevMan Web (RevMan Web 2019). Any disagreements or inconsistencies in data extraction will be resolved by discussion.

Assessment of risk of bias in included studies

Two of the four review authors (TB, DP, SEY, BG) will assess all included studies for risk of bias using Cochrane's risk of bias tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements or inconsistencies in risk of bias assessment will be resolved by discussion. We will assess each of the following seven domains as at low, high, or unclear risk of bias.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other potential threats to validity

When assessing selective reporting bias, where a study does not appear to report all expected results, we will search for the trial protocol to ascertain whether the outcomes were measured but not reported.

For cluster-randomised trials, we will consider the following particular biases based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials (Higgins 2021).

We will report our judgements for each individual study in the risk of bias tables in the 'Characteristics of included studies' section. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

For dichotomous data, we will present the results using risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, we will present the results as a mean difference (MD) with 95% CIs based on the methods described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Where studies do not use the same scales, we will present the results as a standardised mean difference (SMD) with 95% CIs. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

For RCTs we will consider each participant as the unit of analysis. If we identify and include any cluster-randomised trials, we will adjust their sample size using the methods described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), employing an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial. We will combine the results from both individual and cluster-randomised trials, where appropriate, and perform a sensitivity analysis to investigate the effects of the randomisation unit. We will avoid double-counting of participants by accounting for multiple treatment arms.

Dealing with missing data

In the case of any unexplained missing data, we will attempt to contact the study authors. We will use the calculator within Review Manager 5 to calculate missing standard deviations using other data from the trial, such as CIs, employing the methods described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Where this is not possible,

we will consider imputing data; for example, in the case of lack of any variance data for a continuous outcome, we will consider calculating a correlation coefficient from another trial. For all outcomes, we will follow intention-to-treat principles by prioritising the use of analysis with the largest number of participants randomised to each group, only using analyses based on participants that complete the study as a last resort. Where necessary, we will carry out sensitivity analyses within meta-analyses to assess the impact of including studies with unexplained missing data or those with imputed data.

Assessment of heterogeneity

We will visually inspect forest plots to consider the direction and magnitude of effects and the degree of overlap between CIs. We will use the I^2 statistic to measure heterogeneity whilst acknowledging that in the case of a small number of studies there is substantial uncertainty in the value of the I^2. As strict thresholds for the interpretation of I^2 are not recommended, we will use the rough guide to interpretation provided in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

When the I^2 value lies in an area of overlap between two categories (e.g. between 50% and 60%), we will consider differences in participants and interventions amongst the trials in the meta-analysis.

Assessment of reporting biases

In order to reduce the chance of reporting biases, we will search multiple sources. We will assess the presence of publication bias and other reporting bias using funnel plots if sufficient studies (i.e. more than 10) are identified for inclusion in the meta-analysis according to the methods described in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Data synthesis

We will synthesise the data using the methods described in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We will undertake meta-analysis only if it is appropriate to do so (i.e. when the characteristics of the interventions, comparators, participants, and outcomes are similar enough for pooling to be appropriate). We anticipate that the included studies will be a mix of studies: some studies will aim to scan all participants for signs of DVT, and some studies will not scan all but instead assess only participants who present with symptoms. We will therefore consider the various definitions of VTE outcomes reported within studies and how we will synthesise these two types of studies. In the case of substantial heterogeneity, we will use a random-effects meta-analysis; otherwise, we will proceed with fixed-effect meta-analysis. If there is substantial clinical, methodological, or statistical heterogeneity across trials that makes meta-analysis inappropriate, we will synthesise the data using a narrative approach.

Subgroup analysis and investigation of heterogeneity

We plan to investigate the following subgroups for the primary outcomes providing we obtain adequate relevant data.

Interventions

- Preoperative versus postoperative initiation of intervention
- Standard versus extended-duration intervention
- Different doses of the same drug
- Above- versus below-knee stockings
- Full-leg versus below-knee IPC device
- Mobilisation post-hip fracture surgery (early versus late)

Participant characteristics

- Risk for VTE (stratified by high/low using a validated tool such as the Department of Health risk assessment tool which includes age and comorbidities as risk factors)

Other

- Type of non-elective hip fracture surgery (dependent on whether fracture is intracapsular or not) includes: dynamic hip screw, intramedullary hip nailing, hemiarthroplasty, total hip replacement)
- Regional versus general anaesthesia (for hip fracture surgery)
- Timing of hip fracture surgery (< or = 48 hours versus > 48 hours)

Sensitivity analysis

We will perform sensitivity analyses to explore whether the following issues affect the main results: risk of bias, missing data, and including cluster-RCTs, using the methods described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

We will consider the overall risk of bias of an included study as low if there is no high-risk judgement in the four key main domains (random sequence generation, allocation concealment, incomplete outcome data, and selective reporting). Where we have imputed data and where there are unexplained missing data, we will explore the differences between including and excluding these studies within the individual meta-analyses. Where we have included both individually randomised and cluster-randomised trials, we will explore the effects of the randomisation unit by including and excluding cluster-randomised trials. We will consider performing a sensitivity analysis based on date of publication of the study, as we recognise that clinical practice has changed over the years. We will present the results of the sensitivity analyses and compare them with the main overall results.

Summary of findings and assessment of the certainty of the evidence

We will present one summary of findings table for each comparison using GRADEpro GDT software (GRADEpro GDT), in which we will summarise the following main outcomes.

- Venous thromboembolism
- Major bleeding
- All-cause mortality
- Pulmonary embolism
- Deep vein thrombosis

- Infection/re-intervention
- Clinically relevant non-major bleeding

We will assess the certainty of the evidence for each outcome as high, moderate, low, or very low, based on the five GRADE considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias, using the GRADE approach (Schünemann 2021). We will include our justifications for downgrading the certainty of the evidence using footnotes to aid readers' understanding. We will base our conclusions on the certainty of the evidence following GRADE assessment. A draft summary of findings table is provided in Table 1.

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ADDITIONAL TABLES

Table 1. Example summary of findings table

Graduated compression stockings plus low molecular weight heparin (LMWH) compared with LMWH alone to prevent venous thromboembolism after hip fracture surgery

Patient or population: adults aged > 60 years having non-elective surgery for hip fracture

Settings: care setting (hospital, community, care home)

Intervention: graduated compression stockings plus LMWH

Comparison: LMWH

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with LMWH	**Risk with** graduated compression stockings plus LMWH				
Venous thromboembolism [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**	
	[value] per 1000	**[value] per 1000** ([value] to [value])				
Major bleeding [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate**	
	[value] per 1000	**[value] per 1000** ([value] to [value])				

Table 1. Example summary of findings table *(Continued)*

					⊕⊕⊕⊕ **high**
All-cause mortality [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Pulmonary embolism [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Deep vein thrombosis [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Infection/re-intervention [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			

Table 1. Example summary of findings table *(Continued)*

Clinically relevant non-major bleeding [follow-up]	**Study population**		**RR [value]** ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **LMWH**: low molecular weight heparin; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

APPENDICES

Appendix 1. MEDLINE search strategy

1 Pulmonary Embolism/

2 Thromboembolism/

3 Thrombosis/

4 exp Venous Thromboembolism/

5 exp Venous Thrombosis/

6 ((vein* or ven*) adj thromb*).ti,ab.

7 (blood adj3 clot*).ti,ab.

8 deep vein thrombosis.ti,ab.

9 (lung adj3 clot*).ti,ab.

10 (DVT or VTE).ti,ab.

11 peripheral vascular thrombosis.ti,ab.

12 post-thrombotic syndrome.ti,ab.

13 pulmonary embolism.ti,ab.

14 (pulmonary adj3 clot*).ti,ab.

15 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*).ti,ab.

16 venous thromboembolism.ti,ab.

17 or/1-16

18 exp Hip Fractures/

19 ((hip* or femur or femoral or intertrochanteric or subtrochanteric or trochanteric or pertrochanteric or peritrochanteric or acetabul*) adj4 fracture*).ti,ab.

20 or/18-19

21 17 and 20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 drug therapy.fs.

27 randomly.ab.

28 trial.ab.

29 groups.ab.

30 or/22-29

31 exp animals/ not humans.sh.

32 30 not 31

33 21 and 32

CONTRIBUTIONS OF AUTHORS

TB: drafted the protocol, coordinated the protocol process, and takes full responsibility for the overall completion of the review. For the full review TB will acquire trial reports; select trials; extract, analyse, and interpret the data; draft the review and future review updates; and act as a guarantor of the review.
SEY: commented on the draft protocol. For the full review SEY will select trials; extract the data; draft the review and future review updates.
DP: commented on the draft protocol. For the full review DP will select trials; extract, analyse, and interpret the data; draft the review and future review updates.
BG: commented on the draft protocol. For the full review BG will select trials; extract, analyse, and interpret the data; draft the review and future review updates.

DECLARATIONS OF INTEREST

TB: none known
SEY: none known
DP: none known
BG: none known

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NOTES

Parts of the Methods section of this protocol are based on a standard template established by Cochrane Vascular.