Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis

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ABSTRACT

Background: Our aim was to determine the evidence for thromboprophylaxis for prevention of symptomatic venous thromboembolism (VTE) in adults with foot or ankle trauma treated with below knee cast or splint. Our secondary aim was to report major bleeding events.
Methods: MEDLINE and EMBASE databases were searched for randomized controlled trials from inception to 1st June 2015.
Results: Seven studies were included. All focused on low molecular weight heparin (LMWH). None found a statistically significant symptomatic DVT reduction individually. At meta-analysis LMWH was protective against symptomatic DVT (OR 0.29, 95% CI 0.09–0.95). Symptomatic pulmonary embolism affected 3/692 (0.43%). None were fatal. 86 patients required LMWH thromboprophylaxis to prevent one symptomatic DVT event. The overall incidence of major bleeding was 1 in 886 (0.11%).
Conclusions: Low molecular weight heparin reduces the incidence of symptomatic VTE in adult patients with foot or ankle trauma treated with below knee cast or splint.

Contents

1. Introduction

Patients with foot and ankle trauma treated with cast or splint immobilization are at risk of venous thromboembolism (VTE) [1]. The most serious complication of this is death from Pulmonary Embolism (PE), which occurs in approximately 1 in 15,000 patients [2]. Although fatal pulmonary embolism is the most serious thromboembolic complication, it is not the only significant adverse event. Approximately 1 in 500 patients will develop a symptomatic PE within 90 days of injury [2]. Many of these patients will be functionally impaired at long term follow up [3]. The other significant complication is symptomatic deep venous thrombosis, which occurs in approximately 1 in 250 patients with non-operatively treated foot and ankle trauma [4]. 20–50% of these patients will develop post thrombotic syndrome [5]. This condition

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is difficult to treat and therefore it is important to avoid. Considering that lower limb casts and splints are commonly used for a variety of soft tissue and bony traumatic conditions, the population of patients at risk of developing VTE is significant. In view of this, NICE guidelines recommend that patients with foot and ankle trauma and lower limb immobilization should be assessed for risk of development of VTE, and provided with chemical thromboprophylaxis if they have additional risk factors (including cancer, thrombophilia, previous venous thrombosis) [1]. Prophylactic options include either chemical or mechanical methods.

Our aim was to determine the current evidence for the use of chemical or mechanical thromboprophylaxis in the prevention of symptomatic venous thromboembolism in adult patients with foot or ankle trauma treated with below knee cast or splint immobilization. Our secondary aim was to report episodes of major bleeding associated with thromboprophylaxis.

2. Methods

The OVID interface was used to search MEDLINE and EMBASE databases up to 1st June 2015. The following search strategy, previously used by Roberts et al. (2012) was used [6]: (exp venous thrombosis OR exp thromboembolism OR exp pulmonary embolism OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb$.mp) AND (exp casts surgical OR plaster cast$.mp OR exp immobilization OR immobilization.mp). The search was limited to randomized controlled trials, with no language exclusions. One author performed the study selection based on the following defined inclusion and exclusion criteria. Inclusion criteria: Studies including adult patients of any venous thrombo-embolism risk stratification (including operative and non-operative treatment) with foot or ankle trauma treated with below knee cast or immobilizing splint. Study interventions were chemical or mechanical thromboprophylaxis started within 72 h of injury, with a control group, which had no thromboprophylaxis. The outcomes of efficacy were symptomatic venous thrombo-embolism (pulmonary embolism and deep vein thrombosis) objectively proven with imaging. The outcomes of safety were:

1. Major bleeding i.e. bleeding resulting in death, risk to life or blood transfusion.
2. Clinically important non-major bleed i.e. bleeding that required withdrawal from the study.
3. Minor bleed i.e. any other type of bleed which was not major or clinically important.

Only full papers were reviewed. For trials that reported results in more than 1 publication, data from the most complete publication was extracted and used the other publications to clarify the data. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting of systematic reviews and meta-analyses of randomized clinical trials was followed. Two reviewers performed data extraction independently using standardized data extraction sheets. Discrepancies between the reviewers were reviewed by a third reviewer. Odds ratio and absolute risk reduction for symptomatic DVT were used to calculate number needed to prevent with thrombo-prophylaxis. Mantel Haenszel method was used to assess dichotomous outcomes. Statistical heterogeneity was determined using I^2 statistics. Fixed effects model was used when heterogeneity was <30%, using Review Manager (RevMan 5.0).

The risk of bias for each article was determined by two authors, who independently reviewed the full articles. Data was extracted from articles and a judgement with supporting information was made according the Cochrane Risk of Bias tool. In cases where authors disagreed, the evidence for the judgement was discussed and a consensus opinion was reached. A score from 1 to 3 was given for each of the 7 parameters. Where an item was deemed low risk of bias, a score of 1 was given for the item. A score of 2 was given if the risk of bias was deemed unclear. A score of 3 was given if the item was deemed high risk. The lowest risk of bias score for the 7 items was 7. The highest score was 21. Studies were ranked in decreasing order of risk of bias. Where assessors of outcome were not blinded to intervention group, the study was rated as high risk of bias.

3. Results

Seven prospective randomized controlled trials were included in this review (Table 1). Study details are displayed in Table 2. All of these studies focused on chemical thromboprophylaxis. Only two studies considered patients treated non-operatively [7,8], with all others including patients who underwent surgery. One focused on patients with ankle fractures [9], one focused on Achilles tendon ruptures [10], and the remaining 5 studies include patients with a variety of soft tissue and bony injuries [7,8,11–13]. Included studies did not provide details of numbers of patients with individual risk factors for venous thromboembolism.

The most important additional VTE risk factors for patients with cast immobilization are: lower limb cast immobilization, current hormone replacement therapy/oral contraceptive pill, personal or first degree relative history of VTE, active smoker, any recent hospital admission or major surgery, pregnancy or immediate postpartum, any serious co-morbidity including cardiac failure, chronic obstructive pulmonary disease, chronic renal failure or inflammatory bowel disease, extensive varicosities, active cancer, obesity (BMI >30), known thrombophilia, age >60 years [1]. Considering these risk factors, all of the studies included at least some patients who would be considered at increased risk for VTE (Table 2). In 3 studies, patients were recruited within 72 h of injury [9,13]. Lassen et al. recruited patients within 4 days of injury [12]. In the study by Kock et al., the time to recruitment was not stated, however all patients underwent imaging to exclude DVT prior to entering the study [7]. In two studies, the time between injury and recruitment is not stated [8,11]. It is therefore possible that some patients in these studies may have developed asymptomatic DVT prior to entering the study.

All included studies focused on low molecular weight heparin as the intervention: Subcutaneous Dalteparin 5000 international units once daily [9,13], Subcutaneous Tinzaparin (Innohep) 3500 international units once daily [14], 1750 anti-Xa units of reviparin (Clivarine, Knoll) subcutaneous once daily [12], LMWH (Mono-Embolex) daily s/c injection 32 mg [7], LMWH 36 mg injection once daily [8]. Some of these studies included overweight patients, and without dose adjustment for body weight it is possible that doses may have been sub prophylactic in some patients [7,8].

All chemical thromboprophylaxis studies used venography to confirm asymptomatic DVT, except for the most recent study by Selby et al. [13]. It is important to recognize that technological advances and increased operator experience in the use of non-invasive duplex ultrasonography has made this commonplace. Venography has generally been replaced by ultrasound which is more economical, less invasive and safer [15–17]. In the hands of an experienced operator, ultrasonography has a sensitivity of 100%, specificity of 98% and accuracy of 98% for patients with lower limb DVT when compared with venography [18]. In the most recent study, duplex ultrasound was used to image the lower limb venous system [13].

Table 1
Flow diagram of excluded and included studies.

Author	Year	Title	Journal	Reason for exclusion
Samama CM, Lecoules N, Kierzek G, Claessens YE, Riou B, Rosencher N, Mismetti P, Sautet A, Barrellier MT, Apartsin K, Jonas M, Caeiro JR, van der Veen AH, Roy PM; FONDACAST Study Group.	2013	Comparison of fondaparinux with low molecular weight heparin for venous thromboembolism prevention in patients requiring rigid or semi-rigid immobilization for isolated non-surgical below-knee injury.	J Thromb Haemost. 2013 Oct;11(10):1833–43. doi: 10.1111/jth.12395.	Study does not have a control group
Kujath P, Spannagel U, Habscheid W.	1993	Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb	Haemostasis. 1993 Mar;23 Suppl. 1:20–6.	Duplicate publication
Sultan MJ, Zhing T, Morris J, Kurdy N, & McCollum CN.	2015	Compression stockings in the management of fractures of the ankle: a randomized controlled trial.	The Bone & Joint Journal. 2015; 96-B(8), 1062–1069.	No symptomatic VTE events reported
Domeij-Arverud E, Latifi A, Labruto F, Nilsson G, & Ackermann PW.	2015	Can foot compression under a plaster cast prevent deep-vein thrombosis during lower limb immobilization?	The Bone & Joint Journal 2013; 95-B(9), 1227–1231.	No symptomatic VTE events reported

Studies included $n = 7$

Author	Year	Title	Journal
Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F.	2015	A double-blind, randomized controlled trial of the prevention of clinically important venous thromboembolism after isolated lower leg fractures	J Orthop Trauma. 2015 May;29(5):224–30
Lapidus LJ, Ponzer S, Elvin A, Levander C, Lärfars G, Rosfors S, & De Bri E.	2007	Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study.	Acta Orthopaedica, 78(4), 528–535.
Lapidus LJ, Rosfors S, Ponzer S, Levander C, Elvin A, Lärfars G, de Bri E.	2007	Prolonged Thromboprophylaxis With Dalteparin After Surgical Treatment of Achilles Tendon Rupture: A Randomized, Placebo-Controlled Study	J Orthop Trauma. 2007 Jan;21(1):52–7.
Jørgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R et al.	2002	Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study.	Thrombosis Research, 105(6), 477–480.
Lassen MR, Borris LC, & Nakov RL.	2002	Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization	The New England Journal of Medicine, 347(10), 726–730.
Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, & Hirche H.	1995	Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilization of the leg.	The Lancet, 346(8973), 459–461.
Spannagel U, & Kujath P.	1993	Low molecular weight heparin for the prevention of thromboembolism in outpatients immobilized by plaster cast	Seminars in Thrombosis and Hemostasis, 19 Suppl 1, 131–141.

Records identified through database searching $n = 147{,}812$.
Limiting search to randomized controlled trial $n = 1723$.
After duplicates removed $n = 1364$.
Records screened $n = 1364$.
Records excluded $n = 1353$.
Full text articles assessed for eligibility $n = 11$.
Full text articles excluded, with reasons $n = 4$.

3.1. Symptomatic venous thromboembolic outcomes

Five of the seven studies presented data on symptomatic DVT events [8,9,11–13] (Table 3). 2 of these studies reported no symptomatic events in control of intervention groups and were excluded from meta-analysis (Table 4) [7,11]. Considering the 5 studies presenting symptomatic DVT data, the overall incidence was 11/697 (1.58%) in the control group. Considering the 3 studies included in the meta-analysis (Table 4) none of these studies found a statistically significant symptomatic DVT reduction individually, however at meta-analysis of pooled results there was a statistically significant reduction in symptomatic DVT in the patients who received LMWH (OR 0.29, 95% CI 0.09–0.95) [9,12,13].

Six studies presented data for symptomatic pulmonary embolism [8–13] (Table 5). The highest symptomatic Pulmonary Embolism occurrence was 1%, found in the study by Lassen et al. [12]. The overall symptomatic pulmonary embolism rate considering studies presenting this data was 3/692 (0.43%). None of these pulmonary emboli were fatal. LMWH did not result in statistically significant reductions in symptomatic pulmonary emboli in any of these studies or on meta-analysis (Table 6).

3.2. Bleeding events

All 7 studies reported major bleeding, with one non-fatal retroperitoneal haemorrhage event occurring in the study by Lassen et al. [12] (Table 7). Considering the total number of patients who received LMWH in these studies, the overall incidence of major bleeding was 1 in 886 (0.11%), number needed to harm = 886. Considering that the number needed to prevent symptomatic DVT was found to be 86, 10 symptomatic DVT events would be prevented for every major bleed. Clinically relevant non-major and minor bleeds were more likely to occur in the LMWH groups (Tables 8 and 9) however at meta-analysis the 95% confidence interval crossed 1 in both cases and therefore the difference in bleeding event rates for these outcomes was not statistically significant.

3.3. Risk of bias assessment

None of the studies were free of risk of bias (Table 10). The study deemed to be at least risk of bias was by Lassen et al. This study was generally low risk of bias, however there were no details provided

Table 2
Details of included prospective randomized controlled trials.

Study	Year	Injuries included and total number of participants	Participants included (VTE risk factors)	Exclusion criteria	Treatment	Treatment group intervention	Control	Time between injury and recruitment	Outcome measure	Method of objective confirmation of VTE
Selby, R. et al.	2015	Operated lower limb trauma (tibia, fibula, ankle ± associated foot or patella fractures)	Age 18–87 years Surgery BMI not stated OCP not stated Smoking status not stated	Major trauma Other anticoagulant use Allergy to LMWH Pregnancy Active cancer Previous VTE Hypercoagulable state Active bleeding or bleeding disorder Intracranial bleed in previous 4 weeks Vascular injury needing repair	All surgical and cast or splint	Dalteparin 5000 and Xa for 14 ± 2 days	Matching placebo 14 ± 2 days	<72 h	Symptomatic VTE within 3 months or asymptomatic proximal DVT on lower limb venous ultrasound at 14 days	Lower limb venous ultrasound
Lapidus, L.J., Ponzer, S. et al.	2007	Operatively treated ankle fractures (n = 272)	18–75 years All operated	Inability or refusal to sign consent Inability to comply (dementia, alcoholism) Current anticoagulants Allergy to contrast Planned follow up at another hospital Renal disorders including transplant VTE within 3 months Surgery within 1 month Malignancy Current bleeding disorder Pregnancy Aspirin use >325 mg or other platelet inhibitors Polytrauma	Surgery and cast	1000 ml Dextran 60 on admission for all patients, Dalteparin subcut 5000 IU once daily for 1 week for all patients, then randomized to continue or placebo until plaster removed at 5 weeks post surgery	Placebo in identical syringe to intervention	Within 72 h of injury	Asymptomatic at time of cast removal	All patients had phlebography on operated limb only, on day of cast or splint removal. Colour duplex was done is phlebography failed.–All duplex done by 1 of 4 vascular technologists. Also did venography if clinical VTE during study period. CTPA or V/Q if PE clinically suspected
Lapidus, L.J., Rosfors, S. et al.	2007	Achilles tendon ruptures (n = 105)	18–75 years Surgical treatment	Refusal or inability to consent Ongoing anticoagulants Contrast allergy Intended follow up in alternative hospital Inability to comply with study Renal disorder Recent VTE within 3 months Surgery in preceding month Malignancy Bleeding disorder Pregnancy High dose aspirin or platelet inhibitors	Surgery with a postoperative cast or orthosis for 6 weeks	Dalteparin 25,000 units anti Xa/ml, 5000 Unit dose once daily injection	Placebo injection with 0.9% saline in an identical syringe, 6 weeks supply	Within 72 h of injury	Asymptomatic and symptomatic VTE	Unilateral colour duplex USS followed by plethysmography for confirmation if duplex positive
Jorgensen, P.S. et al.	2002	Fracture and tendon injuries (n = 300)	Planned lower limb cast for at least 3 weeks Oral contraceptive pill Previous DVT Smokers Varicose veins Surgery	Pregnancy Allergy to heparin or contrast media Renal or liver impairment Uncontrolled hypertension Bleeding disorders Cerebral insults due to bleeding GI bleeding Inability to perform self-injection	All patients had below knee casts. 86pts in Innohep group had surgery, 89 pts in control had surgery. Injury demographics and surgery was not significantly different between groups.	3500 IU anti Xa tinzaparin (Innohep) s/c once daily for total casting period – mean duration was 5.5 weeks	Nothing	Not stated	Asymptomatic DVT	Unilateral ascending venography
Lassen, M.R. et al.	2002	Fractures (tibia, patella, malleoli, foot), Achilles tendon rupture (n + 438)	Age up to 56 years BMI up to 28 Previous VTE Varicose veins OCP use HRT use Surgery Casts Smokers	Body weight <35 kg Current VTE Systolic BP >200 mmHg or diastolic >110 Cerebral aneurysm CVA within 3 weeks Active GI ulcer Haemorrhagic diathesis Bacterial endocarditis Platelets <100,000 per cubic mm Previous heparin use Immobilization A days prior to enrolment Heparin or contrast allergy Contraindication to venography	Surgery or cast immobilization	1750 anti-Xa units of reviparin (Clivarine, Knoll) subcut to be injected once daily whilst immobilized	The patients received identical prefilled syringes with placebo to take once daily for time of immobilization	Within 4 days of injury	Symptomatic or asymptomatic VTE	ascending venography of the injured leg within one week after removal of the plaster cast or brace. Venography was performed earlier if there was a clinical suspicion of thrombosis

Table 2 (*Continued*)

Study	Year	Injuries included and total number of participants	Participants included (VTE risk factors)	Exclusion criteria	Treatment	Treatment group intervention	Control	Time between injury and recruitment	Outcome measure	Method of objective confirmation of VTE
Kock, H.J. et al.	1995	Fractures or sprains	Age up to 65 years Obesity (Broca index >1.2) Varicose veins Smokers OCP Cast	Surgical treatment Previous DVT Pregnancy Clotting disorders or anticoagulant medication Bleeding sources Chronic venous insufficiency Contra-indication to heparin	Non-operative treatment with cast	LMWH (Mono-Embolex) daily s/c injection 32 mg for duration of cast	Nothing	Not stated – but all had imaging to exclude DVT prior to randomization	Asymptomatic DVT	Ultrasound and phlebography
Spannagel, U. et al.	1993	Fractures, soft tissue injuries	Age up to 76 years Cast Smoking Overweight (110% Broca) Previous thrombosis Varicose veins Malignant disease OCP Pregnancy Heart failure	Hypersensitivity to heparin Thrombopathy Treatment with oral anticoagulation or platelet inhibitors Acute cerebral or GI bleeding Acute pancreatitis Inflammatory heart disease Arterial hypertension (diastolic more than 120 mmHg) Renal failure (serum creatinine 3 mg/dL or greater)	Non-operative soft tissue and bony injury with plaster cast for at least 7 days If patients went on to have operation they were scanned prior to this and exited the study	LMWH 36 mg injection once daily for period of cast	Nothing	Not stated	All were scanned. Asymptomatic DVT. Some had symptoms at time of scanning (33.3% of those with positive scans, but criteria for 'symptomatic' not defined)	Compression ultrasound on cast removal Phlebography on cases of positive compression ultrasound

Table 3
Symptomatic DVT.

Study	Intervention (*n*)	Symptomatic DVT (total)	Control	Symptomatic DVT (total)
Kock 1995	176	0	163	0
Lassen 2002	189	0	191	4
Jorgensen 2002	99	0	106	0
Lapidus Ankle 2007	117	2	109	6
Selby 2015	130	1	128	1
Total	711	3	697	11

Number needed to prevent one symptomatic DVT = 1/((711−3)/711)−((697−11)/697) = 86.

in the paper of the method of group allocation concealment [12]. The study by Lapidus and Ponser [9] scored a 3 'high risk of bias' in the category of 'Other' because all patients (those in intervention and those in control) received LMWH for 1 week prior to being randomized. It is possible that this may have reduced the effect size of the LMWH provided to the intervention group after randomization. We deemed the studies by Kock and Spannagel [7,8] to be at highest risk of bias overall. Also, these studies did not state whether assessors of outcome of DVT were blinded to participant intervention group. The results of these studies should be viewed with caution.

4. Discussion

Orthopaedic surgical patients are generally regarded as high risk of venous thromboembolic complications. Patients undergoing surgery for hip fracture, total hip or knee replacement have deep vein thrombosis incidences of up to 60% [1]. Prevention of VTE is more desirable than treating VTE events from both a clinical and financial perspective [19], and there is no doubt that mechanical and chemical thrombo prophylaxis are effective in patients undergoing major Orthopaedic surgery. For example, in the context of total knee replacement, the addition of mechanical to chemical thromboprophylaxis (pneumatic compression) significantly reduces the incidence of DVT from 18.7% to 3.7% with combined prophylaxis. The effects are similar for patients undergoing total hip replacement (reduction in DVT from 9.71% to 0.94%) [20]. In patients who undergo hip fracture surgery, heparin or mechanical thromboprophylaxis with foot or calf pumping devices are also effective in reducing the incidence of DVT [21]. In view of this, it has become accepted that patients undergoing major Orthopaedic surgery should be provided with thrombo prophylaxis unless contra-indicated.

Another group of patients which account for a large workload for the Orthopaedic surgeon are patients with foot and ankle trauma. Many of these patients are treated as outpatients, non-surgically with casts or splints. Some studies indicate that these patients are also at increased risk of venous thrombo-embolism due to a combination of patient, injury and treatment factors [8]. In the United Kingdom, it is recommended that all patients treated with cast or splint immobilization should be assessed for risk of venous thrombo-embolism and provided with thrombo prophylaxis where increased risk is identified [1]. Some authors recommend thromboprophylaxis for all patients with immobilization of the lower extremity, irrespective of age and other risk factors [8,22]. In some U.K. hospitals, all patients treated with lower limb immobilization are provided with chemical thromboprophylaxis. It has been reported that this practice is cost effective when considering the potential savings in litigation [23]. This may be true, however it is vital to review the evidence of the effects of thromboprophylaxis in patients with lower limb cast or splint immobilization to enable clinicians to make informed decisions for or against its use.

Table 4
Symptomatic DVT meta-analysis.

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lapidus Ankle 2007	2	117	6	109	52.8%	0.30 [0.06, 1.51]
Lassen 2002	0	189	4	191	38.6%	0.11 [0.01, 2.06]
Selby 2015	1	130	1	128	8.6%	0.98 [0.06, 15.91]
Total (95% CI)		**436**		**428**	**100.0%**	**0.29 [0.09, 0.95]**
Total events	3		11			

Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%

Test for overall effect: Z = 2.04 (P = 0.04)

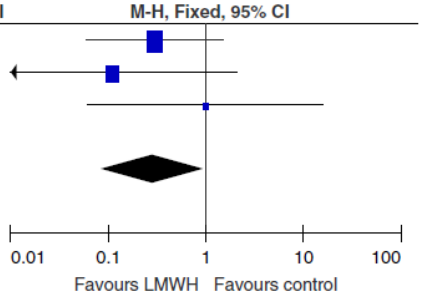


Table 5
Symptomatic pulmonary embolism.

Study	Intervention (*n*)	Symptomatic PE	Control	Symptomatic PE
Kock 1995	176	0	163	0
Spannagel 1993	126	0	127	0
Lassen 2002	217	0	221	2
Jorgensen 2002	99	0	106	0
Lapidus Ankle 2007	117	0	109	0
Lapidus Achilles 2007	49	0	47	0
Selby 2015	130	0	128	1
Total	914	0	901	3

Table 7
Major bleeding events.

Study	Intervention	Major bleed	Control	Major bleed
Kock 1995	176	0	163	0
Spannagel 1993	126	0	127	0
Lassen 2002	189	1	191	0
Jorgensen 2002	99	0	106	0
Lapidus Ankle 2007	117	0	109	0
Lapidus Achilles 2007	49	0	47	0
Selby 2015	130	0	128	0

Considering studies which reported symptomatic venous thrombo-embolism, deep vein thrombosis occurred in 1.58% of patients randomized to no prophylaxis group (11/697) [7,9,11–13] (Table 3). Symptomatic pulmonary embolism occurred in 0.33% of patients (3/901) [7–9,12,13] (Table 5). The most serious complication of this is death from Pulmonary Embolism (PE), which has recently been shown to occur in approximately 1 in 15,000 patients [2]. None of the included studies in this review are therefore adequately powered to assess a reduction in this outcome. It is therefore not surprising that there is uncertainty amongst Orthopaedic surgeons on the effectiveness of chemical thromboprophylaxis to prevent fatal PE [24].

All studies included in this review focused on the effects of chemical thromboprophylaxis ($n = 7$). All focused on low molecular weight heparin. None considered alternatives such as aspirin or newer oral anticoagulant direct thrombin inhibitors. None of the included studies found a significant reduction in symptomatic DVT

Table 6
Symptomatic pulmonary embolism meta-analysis.

Study or Subgroup	Thromboprophylaxis Events	Thromboprophylaxis Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jorgensen 2002	0	99	0	106		Not estimable
Kock 1995	0	176	0	163		Not estimable
Lapidus Achilles 2007	0	49	0	47		Not estimable
Lapidus Ankle 2007	0	117	0	109		Not estimable
Lassen 2002	0	217	2	221	62.1%	0.20 [0.01, 4.23]
Selby 2015	0	130	1	128	37.9%	0.33 [0.01, 8.07]
Spannagel 1993	0	126	0	127		Not estimable
Total (95% CI)		**914**		**901**	**100.0%**	**0.25 [0.03, 2.24]**
Total events	0		3			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

Test for overall effect: Z = 1.24 (P = 0.21)

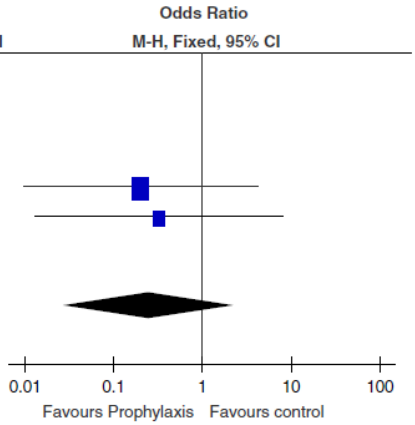


Table 8
Clinically relevant non-major bleed.

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jorgensen 2002	5	99	0	106	18.5%	12.40 [0.68, 227.17]
Lapidus Ankle 2007	1	117	1	109	41.5%	0.93 [0.06, 15.07]
Lassen 2002	1	189	1	191	40.0%	1.01 [0.06, 16.28]
Total (95% CI)		**405**		**406**	**100.0%**	**3.08 [0.74, 12.79]**
Total events	7		2			

Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 1.55 (P = 0.12)

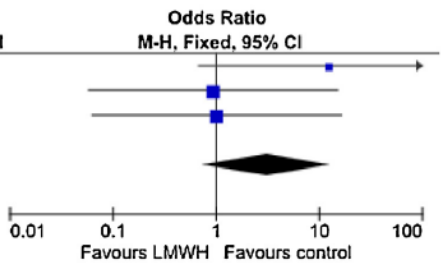
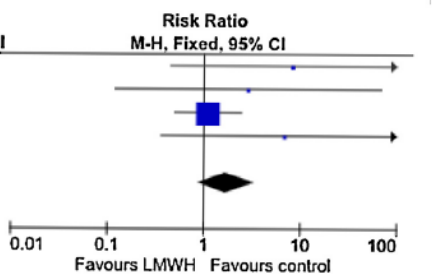


Table 9
Minor bleed.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kock 1995	4	176	0	163	4.2%	8.34 [0.45, 153.69]
Lapidus Achilles 2007	1	49	0	47	4.1%	2.88 [0.12, 68.98]
Lassen 2002	12	189	11	191	87.7%	1.10 [0.50, 2.44]
Selby 2015	3	130	0	128	4.0%	6.89 [0.36, 132.12]
Total (95% CI)		**544**		**529**	**100.0%**	**1.71 [0.86, 3.39]**
Total events	20		11			

Heterogeneity: Chi² = 3.27, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 1.54 (P = 0.12)



at individual study level, however at meta analysis (Table 4), there was a statistically significant reduction (OR 0.29, 95% CI 0.09–0.95) [9,12,13]. The number needed to prevent symptomatic DVT was 86, considering all studies reporting this outcome for each group (Table 4). To put this into context, the numbers needed to prevent recurrent hip fracture in post menopausal women with hip fracture is 100 [25].

It is important to recognize that if there is a delay in commencing thrombo prophylaxis, which may be due to patients presenting several days after their injury, they may have already developed deep vein thrombosis. There are no studies that quantify this effect, however the majority of RCT's included in this review recruited patients within 3 days of injury. In a study of thrombo prophylaxis in patients with acute stroke, both leg Doppler USS performed at 3 days following admission found that 8% had already developed an asymptomatic DVT [26]. Another important consideration is that patients must comply with LMWH injections in order to achieve reductions in venous thromboembolism. Some studies suggest that 12% of patients stop taking LMWH due to discomfort [14]. In a prospective study of 214 patients of mean age 34 years, using enoxaparin injections in France, 20.5% were deemed inappropriate for training or refused, with a further 12% failing to use LMWH after being trained to perform injections [27]. This will significantly affect the efficacy of prophylaxis in clinical practice.

The main strength of our review is that we have only included level 1 evidence studies. The benefit of this is that randomization equalizes both known and unknown confounding variables between groups [28]. We also focused on VTE events and major bleeding, because the clinical importance of these outcomes is not controversial. We were unable to determine the precise numbers of patients with additional risk factors for VTE in the included studies because this level of detail was not available from the full texts. This may have influenced the results of studies. A further limitation of our study is the low number of studies included for meta-analysis. This reflects the lack of high level of evidence studies available and is an area for future research. Furthermore, none of the studies found significant effects of thromboprophylaxis and are likely to be underpowered. Future studies should include sufficient participant numbers to detect true differences between groups and thus the most appropriate way we should be managing these patients. As such, our findings and conclusions represent a useful overview of our current understanding of VTED in this population, but given the many limitations of the available science for analysis must still be interpreted with caution until better data become available'.

We conclude that LMWH reduces the incidence of symptomatic VTE events in patients with lower limb trauma and below knee cast treatment. However, there is a risk of major bleeding (0.11%) which needs to be carefully considered against the benefit of prevention of symptomatic VTE events. Considering that the number needed to prevent symptomatic DVT was found to be 86, 10 symptomatic DVT events would be prevented for every major bleed. The clinical and financial implications of this require further prospective study. It is also vital to identify which patients in casts are most likely to develop VTE, to enable thrombo prophylaxis to be prescribed accurately to those at highest risk. We suggest multi centre studies are necessary to achieve definitive answers. Current guidelines will make such studies difficult, due to recommendation for thrombo prophylaxis in many patients with casts and perceived additional VTE risk factors.

Table 10
Risk of bias assessment.

Study	Year	Selection bias – random sequence generation	Selection bias – allocation concealment	Performance bias – blinding of participants and personnel	Detection bias – blinding of outcome assessment	Attrition bias – incomplete outcome data	Reporting bias – selective reporting	Other bias	Total risk of bias score
Selby, R. et al.	2015	Randomization using a computer randomization code Low risk of bias (1)	Medications were pre-packaged by study sponsor and distributed by them Low risk of bias (1)	Patients and all research personnel were blinded to the study medication. However, does not state that study/placebo were identical Unclear risk (2)	Bilateral Doppler ultrasound by certified vascular technologist with confirmation by staff radiologist, both blinded Low risk (1)	Compliance assessed by syringe count. Clear about who was lost and why Low risk of bias (1)	Made it clear that they only looked at clinically important venous thromboembolism events Low risk of bias (1)	Nil. Low risk of bias (1)	8
Lassen, M.R. et al.	2012	Randomization was performed by computer in blocks of four Low risk of bias (1)	No details of allocation concealment Unclear risk (2)	Control group received identical placebo injection. All the data were collected by a Danish contract research organization and transferred to the statistical department of the sponsor Low risk of bias (1)	Review of venography centrally by 3 radiologists blinded to group Low risk of bias (1)	4 patients dropped out due to adverse events but not stated what these events were Unclear risk of bias (2)	Reported that one patient had venogram more than 1 week after cast removal and excluded this because it did not meet inclusion, which was good. Reported on planned outcome measure. Low risk of bias (1)	Malleolar fractures significantly less common and Achilles tendon rupture more common in LMWH group Unclear risk of bias (2)	10
Lapidus, L.J., Ponzer, S. et al.	2007	Randomization method not stated Unclear risk (2)	Allocation concealment not stated Unclear risk (2)	Control group received identical placebo injection pen Low risk of bias (1)	An independent radiologist who was blinded to the randomization Low risk of bias (1)	All patients accounted for Low risk of bias. 75/272 randomized were lost to follow up. Reasons were stated but this is high (28%). (1)	All patients accounted for and intention to treat analysis done for primary outcome i.e. venographic DVT Low risk of bias (1)	All patients received LMWH for a week before randomization, which could have equalized the results. This was felt to be necessary ethically High risk of bias in a sense that LMWH effect size could have been reduced between groups after randomization (3)	11
Lapidus, L.J., Rosfors, S. et al.	2007	Consecutive recruitment computer randomization (1)	Not stated Unclear risk (2)	All participants got an identical injection (control was placebo) Low risk of bias (1)	Radiologist blinded to randomized group Low risk of bias (1)	All accounted for Low risk of bias (1)	Secondary analysis was done based on USS endpoint whereas it was planned that USS + phlebo Unclear risk of bias (2)	This study is likely to be underpowered High risk (3)	11
Jorgensen, P.S. et al.	2002	Random numbers in sealed envelopes – details of randomization sequence not given Low risk of bias – randomization appeared to work (1)	Sealed envelopes. Not stated when patients were allocated Unclear risk of bias (2)	Control group did not receive anything therefore may have known which group they were in. Patients were therefore unlikely to be blinded. Unclear risk. Even if patients knew which group they were in, I don't think this would influence outcome (2)	Two experienced radiologists, independent of treatment group assessed venograms. Assessor blinded. Low risk of bias (1)	Although all randomized participants were accounted for, the loss to follow up was very high (32% i.e. 95/300 lost). The study is therefore underpowered. High risk of bias due to inadequate participants completing study, making it underpowered to detect a significant difference (3)	No flow diagram. Difficult to follow how and why patients were lost through study. Unclear risk (2)	With such a high rate of patient withdrawal from study due to injections, how did they check compliance with injections? Unclear risk of bias (2)	13
Spannagel, U. et al.	1993	Not stated Unclear risk of bias (2)	Not stated Unclear risk of bias (2)	Not stated if sonographers were blinded to group Control did not receive a placebo injection Unclear risk of bias (2)	Not stated if sonographers were blinded to group Unclear risk of bias (3)	306 randomized. 53 excluded (14 in control got LMWH by someone else, 12 in LMWH group stopped it on own accord, 3 casts removed before 7 days, 6 underwent surgery before 7 days in cast, 18 casted patients did not return for any follow up!). Therefore 253 included. Low risk of bias (all accounted for. 17% lost, therefore still high quality (1))	USS was performed to detect DVT, then phlebography to confirm. Phlebographic rates slightly lower. Authors chose to present USS rates. Unclear risk (2)	They have done stats on multiple outcome measures, Not stated if they used Bonferroni correction Unclear risk (2)	14 Not stated if assessors were blinded to treatment group
Kock, H.J. et al.	1995	Randomized with lists stratified for varicose veins and obesity (>20% above ideal Broca weight) Unclear risk of bias (2)	Not stated Unclear risk of bias (2)	Control did not get a placebo injection because it was felt to be unethical. Therefore patients were unlikely blinded Unclear risk of bias (2)	Not stated if assessors of DVT imaging were blinded Unclear risk of bias (3)	Its unclear how many patients were randomized and subsequently were lost to follow up Unclear risk of bias (2)	Primary outcome was reported Low risk of bias (1)	Significantly more patients in control group on OCP and significantly longer duration of cast in control group also High risk of bias (3)	15 Not stated if assessors were blinded to treatment group

Conflicts of interest statement

None declared.

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