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Treatment for superficial thrombophlebitis of the leg (Review)

Di Nisio M, Wichers IM, Middeldorp S

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	8
OBJECTIVES	8
METHODS	8
RESULTS	10
Figure 1.	11
Figure 2.	13
DISCUSSION	17
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	19
REFERENCES	20
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	57
Analysis 1.1. Comparison 1 Fondaparinux versus placebo, Outcome 1 Pulmonary embolism.	57
Analysis 1.2. Comparison 1 Fondaparinux versus placebo, Outcome 2 Deep vein thrombosis.	58
Analysis 1.3. Comparison 1 Fondaparinux versus placebo, Outcome 3 Deep vein thrombosis or pulmonary embolism.	58
Analysis 1.4. Comparison 1 Fondaparinux versus placebo, Outcome 4 Extension of superficial thrombophlebitis.	58
Analysis 1.5. Comparison 1 Fondaparinux versus placebo, Outcome 5 Recurrence of superficial thrombophlebitis.	58
Analysis 1.6. Comparison 1 Fondaparinux versus placebo, Outcome 6 Mortality.	58
Analysis 1.7. Comparison 1 Fondaparinux versus placebo, Outcome 7 Major bleeding.	59
Analysis 1.8. Comparison 1 Fondaparinux versus placebo, Outcome 8 Clinically relevant non-major bleeding.	59
Analysis 1.9. Comparison 1 Fondaparinux versus placebo, Outcome 9 Minor bleeding.	59
Analysis 1.10. Comparison 1 Fondaparinux versus placebo, Outcome 10 Arterial thromboembolic complication.	59
Analysis 1.11. Comparison 1 Fondaparinux versus placebo, Outcome 11 Adverse effects of treatment.	59
Analysis 1.12. Comparison 1 Fondaparinux versus placebo, Outcome 12 Non-fatal serious adverse event.	59
Analysis 2.1. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 1 Pulmonary embolism.	60
Analysis 2.2. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 2 Deep vein thrombosis.	60
Analysis 2.3. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 3 Deep vein thrombosis or pulmonary embolism.	61
Analysis 2.4. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 4 Extension of superficial thrombophlebitis.	61
Analysis 2.5. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 5 Recurrence of superficial thrombophlebitis.	61
Analysis 2.6. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 6 Mortality.	61
Analysis 2.7. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 7 Major bleeding.	61
Analysis 2.8. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 8 Clinically relevant non-major bleeding.	62
Analysis 2.9. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 9 Minor bleeding.	62
Analysis 2.10. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 10 Serious adverse events.	62
Analysis 2.11. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 11 Adverse effects of treatment.	62
Analysis 3.1. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 1 Venous thromboembolism end-of-treatment.	63
Analysis 3.2. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 2 Venous thromboembolism 3-month follow-up.	63
Analysis 3.3. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.	63
Analysis 3.4. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 4 Major bleeding. ...	63
Analysis 3.5. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 5 Heparin-induced thrombocytopenia.	64
Analysis 4.1. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 1 Venous thromboembolism end-of-treatment.	64
Analysis 4.2. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 2 Venous thromboembolism 3-month follow-up.	64

Analysis 4.3. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.	65
Analysis 4.4. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 4 Major bleeding. ...	65
Analysis 4.5. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 5 Heparin-induced thrombocytopenia.	65
Analysis 5.1. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.	66
Analysis 5.2. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.	66
Analysis 5.3. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.	66
Analysis 5.4. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.	66
Analysis 5.5. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.	66
Analysis 5.6. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.	67
Analysis 6.1. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.	67
Analysis 6.2. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.	67
Analysis 6.3. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.	68
Analysis 6.4. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.	68
Analysis 6.5. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.	68
Analysis 6.6. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.	68
Analysis 7.1. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.	69
Analysis 7.2. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.	69
Analysis 7.3. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.	69
Analysis 7.4. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.	70
Analysis 7.5. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.	70
Analysis 7.6. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.	70
Analysis 8.1. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 1 Symptomatic venous thromboembolism.	71
Analysis 8.2. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 2 Symptomatic pulmonary embolism.	71
Analysis 8.3. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 3 Superficial thrombophlebitis progression into deep vein thrombosis.	71
Analysis 8.4. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 4 Major bleeding.	71
Analysis 9.1. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 1 Superficial thrombophlebitis or venous thromboembolism.	72
Analysis 9.2. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 2 Venous thromboembolism.	72
Analysis 9.3. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 3 Superficial thrombophlebitis.	73

Analysis 9.4. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 4 Swelling disappearance.	73
Analysis 9.5. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 5 Tenderness disappearance.	73
Analysis 9.6. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 6 Pain disappearance.	73
Analysis 9.7. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 7 Pitting oedema disappearance.	73
Analysis 9.8. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 8 Collateral veins disappearance.	74
Analysis 9.9. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 9 Redness disappearance.	74
Analysis 9.10. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 10 Palpable cord disappearance.	74
Analysis 9.11. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 11 Major bleeding.	74
Analysis 9.12. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 12 Heparin-induced thrombocytopenia.	75
Analysis 10.1. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 1 Venous thromboembolism.	75
Analysis 10.2. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	75
Analysis 10.3. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 3 Major bleeding.	76
Analysis 10.4. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 4 Complications.	76
Analysis 11.1. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism.	76
Analysis 11.2. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	77
Analysis 11.3. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Major bleeding.	77
Analysis 11.4. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Heparin-induced thrombocytopenia.	77
Analysis 12.1. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism.	78
Analysis 12.2. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	78
Analysis 12.3. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Major bleeding.	78
Analysis 12.4. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Heparin-induced thrombocytopenia.	79
Analysis 13.1. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism end-of-treatment.	79
Analysis 13.2. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Venous thromboembolism 3-month follow-up.	79
Analysis 13.3. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.	80
Analysis 13.4. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Major bleeding.	80
Analysis 13.5. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 5 Heparin-induced thrombocytopenia.	80
Analysis 14.1. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 1 Pulmonary embolism.	81
Analysis 14.2. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 2 Deep vein thrombosis.	81

Analysis 14.3. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 3 Extension of superficial thrombophlebitis.	81
Analysis 14.4. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 4 Pain reduction.	81
Analysis 14.5. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 5 Hyperaemia reduction.	82
Analysis 14.6. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 6 Tenderness reduction.	82
Analysis 14.7. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 7 Palpable cord reduction.	82
Analysis 14.8. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 8 Mortality.	82
Analysis 14.9. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 9 Major bleeding.	82
Analysis 14.10. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 10 Minor bleeding.	83
Analysis 14.11. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 11 Adverse events.	83
Analysis 15.1. Comparison 15 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.	83
Analysis 15.2. Comparison 15 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	83
Analysis 16.1. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 1 Deep vein thrombosis.	84
Analysis 16.2. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 2 Participants with thrombus at 21 days.	84
Analysis 16.3. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 3 Allergic reaction or elevated sedimentation rate.	84
Analysis 17.1. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 1 Incidence of venous thromboembolism.	85
Analysis 17.2. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	85
Analysis 17.3. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 3 Major bleeding.	85
Analysis 17.4. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 4 Heparin-induced thrombocytopenia.	86
Analysis 18.1. Comparison 18 Heparin calcium plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.	86
Analysis 19.1. Comparison 19 Heparin subcutaneous (sc) versus defibrotide, Outcome 1 Decrease in the analogue score.	86
Analysis 19.2. Comparison 19 Heparin subcutaneous (sc) versus defibrotide, Outcome 2 Adverse effects of treatment.	87
Analysis 20.1. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 1 Venous thromboembolism.	87
Analysis 20.2. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	87
Analysis 20.3. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 3 Major bleeding.	88
Analysis 20.4. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 4 Heparin-induced thrombocytopenia.	88
Analysis 21.1. Comparison 21 Indomethacin versus placebo, Outcome 1 Adverse effects.	88
Analysis 22.1. Comparison 22 Nimesulide versus diclofenac sodium, Outcome 1 Gastric pain.	88
Analysis 23.1. Comparison 23 Essaven gel versus placebo, Outcome 1 Intolerance.	89
Analysis 24.1. Comparison 24 Thrombectomy plus venoruton plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.	89
Analysis 25.1. Comparison 25 Thrombectomy plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.	90
Analysis 26.1. Comparison 26 Ligation plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.	90
Analysis 26.2. Comparison 26 Ligation plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	90

Analysis 27.1. Comparison 27 Prophylactic unfractionated heparin (UFH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.	91
Analysis 27.2. Comparison 27 Prophylactic unfractionated heparin (UFH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	91
Analysis 28.1. Comparison 28 Oral vasotonin versus placebo, Outcome 1 Cured or substantially better.	91
Analysis 28.2. Comparison 28 Oral vasotonin versus placebo, Outcome 2 Poor tolerability.	91
Analysis 29.1. Comparison 29 Elastic compression bandage (ECB) plus venoruton versus ECB alone, Outcome 1 Deep vein thrombosis.	92
Analysis 30.1. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 1 Redness disappearance.	92
Analysis 30.2. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 2 Pain disappearance.	92
Analysis 30.3. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 3 Disappearance of itching.	93
Analysis 30.4. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 4 Oedema improvement.	93
Analysis 30.5. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 5 Trophism improvement.	93
Analysis 31.1. Comparison 31 Oxyphenbutazone versus placebo, Outcome 1 Tenderness improvement.	93
Analysis 32.1. Comparison 32 Vitamin K antagonist (VKA) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.	94
Analysis 32.2. Comparison 32 Vitamin K antagonist (VKA) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	94
Analysis 33.1. Comparison 33 Stripping plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.	94
Analysis 33.2. Comparison 33 Stripping plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.	95
Analysis 34.1. Comparison 34 Enzyme therapy versus placebo, Outcome 1 Pain reduction.	95
Analysis 34.2. Comparison 34 Enzyme therapy versus placebo, Outcome 2 Responders.	95
Analysis 35.1. Comparison 35 Desmin intramuscular (im) 200 versus desmin 100, Outcome 1 Adverse events.	96
Analysis 35.2. Comparison 35 Desmin intramuscular (im) 200 versus desmin 100, Outcome 2 Adverse drug reactions.	96
Analysis 36.1. Comparison 36 Desmin subcutaneous (sc) 2 × 100 versus desmin 100, Outcome 1 Adverse events.	96
Analysis 36.2. Comparison 36 Desmin subcutaneous (sc) 2 × 100 versus desmin 100, Outcome 2 Adverse drug reactions.	96
Analysis 37.1. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 1 Pain (VAS, cm) at 3 weeks.	97
Analysis 37.2. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 2 Skin erythema (cm ²) at 3 weeks.	97
Analysis 37.3. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 3 SF-36 physical score at 3 weeks.	97
Analysis 37.4. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 4 SF-36 mental score at 3 weeks.	98
APPENDICES	98
FEEDBACK	99
WHAT'S NEW	100
HISTORY	100
CONTRIBUTIONS OF AUTHORS	101
DECLARATIONS OF INTEREST	101
SOURCES OF SUPPORT	101
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	101
INDEX TERMS	101

[Intervention Review]

Treatment for superficial thrombophlebitis of the leg

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ABSTRACT

Background

The optimal treatment of superficial thrombophlebitis (ST) of the legs remains poorly defined. While improving or relieving the local painful symptoms, treatment should aim at preventing venous thromboembolism (VTE), which might complicate the natural history of ST. This is the third update of a review first published in 2007.

Objectives

To assess the efficacy and safety of topical, medical, and surgical treatments for ST of the leg in improving local symptoms and decreasing thromboembolic complications.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register (March 2017), CENTRAL (2017, Issue 2), and trials registries (March 2017). We handsearched the reference lists of relevant papers and conference proceedings.

Selection criteria

Randomised controlled trials (RCTs) evaluating topical, medical, and surgical treatments for ST of the legs that included people with a clinical diagnosis of ST of the legs or objective diagnosis of a thrombus in a superficial vein.

Data collection and analysis

Two authors assessed the trials for inclusion in the review, extracted the data, and assessed the quality of the studies. Data were independently extracted from the included studies and any disagreements resolved by consensus. We assessed the quality of the evidence using the GRADE approach.

Main results

We identified three additional trials (613 participants), therefore this update considered 33 studies involving 7296 people with ST of the legs. Treatment included fondaparinux; rivaroxaban; low molecular weight heparin (LMWH); unfractionated heparin (UFH); non-steroidal anti-inflammatory drugs (NSAIDs); compression stockings; and topical, intramuscular, or intravenous treatment to surgical interventions such as thrombectomy or ligation. Only a minority of trials compared treatment with placebo rather than an alternative treatment and many studies were small and of poor quality. Pooling of the data was possible for few outcomes, and none were part of a placebo-controlled trial. In one large, placebo-controlled RCT of 3002 participants, subcutaneous fondaparinux was associated with a significant reduction in symptomatic VTE (risk ratio (RR) 0.15, 95% confidence interval (CI) 0.04 to 0.50; moderate-quality evidence), ST extension (RR 0.08, 95% CI 0.03 to 0.22; moderate-quality evidence), and ST recurrence (RR 0.21, 95% CI 0.08 to 0.54; moderate-quality evidence) relative to placebo. Major bleeding was infrequent in both groups with very wide CIs around risk estimate (RR 0.99, 95% CI 0.06 to 15.86; moderate-quality

Treatment for superficial thrombophlebitis of the leg (Review)

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evidence). In one RCT on 472 high-risk participants with ST, fondaparinux was associated with a non-significant reduction of symptomatic VTE compared to rivaroxaban 10 mg (RR 0.33, 95% CI 0.03 to 3.18; low-quality evidence). There were no major bleeding events in either group (low-quality evidence). In another placebo-controlled trial, both prophylactic and therapeutic doses of LMWH (prophylactic: RR 0.44, 95% CI 0.26 to 0.74; therapeutic: RR 0.46, 95% CI 0.27 to 0.77) and NSAIDs (RR 0.46, 95% CI 0.27 to 0.78) reduced the extension (low-quality evidence) and recurrence of ST (low-quality evidence) in comparison to placebo, with no significant effects on symptomatic VTE (low-quality evidence) or major bleeding (low-quality evidence). Overall, topical treatments improved local symptoms compared with placebo, but no data were provided on the effects on VTE and ST extension. Surgical treatment combined with elastic stockings was associated with a lower VTE rate and ST progression compared with elastic stockings alone. However, the majority of studies that compared different oral treatments, topical treatments, or surgery did not report VTE, ST progression, adverse events, or treatment adverse effects.

Authors' conclusions

Prophylactic dose fondaparinux given for 45 days appears to be a valid therapeutic option for ST of the legs for most people. The evidence on topical treatment or surgery is too limited and does not inform clinical practice about the effects of these treatments in terms of VTE. Further research is needed to assess the role of rivaroxaban and other direct oral factor-X or thrombin inhibitors, LMWH, and NSAIDs; the optimal doses and duration of treatment in people at various risk of recurrence; and whether a combination therapy may be more effective than single treatment. Adequately designed and conducted studies are required to clarify the role of topical and surgical treatments.

PLAIN LANGUAGE SUMMARY

Treatment for superficial thrombophlebitis of the leg

Background

Superficial thrombophlebitis (ST) is a relatively common inflammatory process associated with a blood clot (thrombus) that affects the superficial veins (veins that are close to the surface of the body). Symptoms and signs include local pain, itching, tenderness, reddening of the skin, and hardening of the surrounding tissue. There is some evidence to suggest a link between ST and venous thromboembolism (VTE; a condition where blood clots form (most often) in the deep veins of the leg and can travel in the circulation and lodge in the lungs). Treatment aims to relieve the local symptoms and to prevent the extension of the clot into a deep vein, ST recurrence, or the development of more serious events caused by VTE. This is the third update of a review first published in 2007. The evidence is current to March 2017.

Study characteristics and key results

This update included 33 randomised controlled trials (clinical trials where people are randomly put into one of two or more treatment groups) involving 7296 participants. Treatments included rivaroxaban (a medicine called a direct oral inhibitor of activated factor X), injections of medicines under the skin to prevent blood clotting (e.g. fondaparinux, low molecular weight heparin, or unfractionated heparin), elastic compression stockings, oral non-steroidal anti-inflammatory drugs (NSAIDs; a pain killer medicine), topical treatment (medicine applied to the skin), and surgery.

One large study, accounting for half of the participants included in the review, showed that treatment with fondaparinux for 45 days was associated with a significant reduction in symptomatic VTE (where symptoms indicate there is a VTE), ST extension (where the clot moves further up the leg), and recurrence of ST (where clots return) compared to placebo. Major bleeding was infrequent in both groups. In one study in people with ST at high risk of recurrent thromboembolic events, fondaparinux was associated with a non-significant reduction of symptomatic VTE compared to rivaroxaban. There were no major bleeding events in either group. Both low molecular weight heparin and NSAIDs reduced the occurrence of extension or recurrence of ST with no effect on symptomatic VTE or major bleeding. Topical treatments relieved local symptoms but the trials did not report on progression to VTE. Surgical treatment and wearing elastic stockings were associated with a lower rate of VTE and progression of the ST compared with elastic stockings alone.

Quality of the evidence

Overall, the quality of evidence was very low for most treatments due to poor study design, imprecision of results, lack of a placebo (non-treated) group and only one study in some comparison. The quality of evidence was low to moderate for comparisons in two placebo-controlled trials.

In conclusion, fondaparinux appears to be an adequate treatment for most people with ST. The optimal dose and duration of treatment need to be established in people at high risk as well as people at low risk for recurrent thrombotic events. Further research is needed to assess the role of rivaroxaban and other such medicines, or thrombin, low molecular weight heparin or NSAIDs and to demonstrate the effectiveness, if any, of topical treatment, or surgery in terms of VTE.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fondaparinux compared to placebo for superficial thrombophlebitis of the leg

Fondaparinux compared to placebo for superficial thrombophlebitis of the leg

Patient or population: people with ST of the leg

Settings: hospitalised or non-hospitalised

Intervention: fondaparinux

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Fondaparinux				
Symptomatic VTE Ventilation-perfusion scanning, helical computed tomography, pulmonary angiography, autopsy, ultrasonography, or venography Follow-up: 77 days	13 per 1000	2 per 1000 (1 to 7)	RR 0.15 (0.04 to 0.5)	3002 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Major bleeding Follow-up: 77 days	1 per 1000	1 per 1000 (0 to 11)	RR 0.99 (0.06 to 15.86)	2987 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Extension of ST Ultrasonography Follow-up: 77 days	34 per 1000	3 per 1000 (1 to 7)	RR 0.08 (0.03 to 0.22)	3002 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Recurrence of ST Ultrasonography Follow-up: 77 days	16 per 1000	3 per 1000 (1 to 9)	RR 0.21 (0.08 to 0.54)	3002 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Mortality Follow-up: 77 days	1 per 1000	1 per 1000 (0 to 15)	RR 2 (0.18 to 22)	3002 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Minor bleeding Follow-up: 77 days	4 per 1000	6 per 1000 (2 to 17)	RR 1.49 (0.53 to 4.17)	2987 (1 study)	⊕⊕⊕⊖ Moderate ¹	-
Adverse effects of treatment Follow-up: 77 days	33 per 1000	37 per 1000 (26 to 54)	RR 1.13 (0.78 to 1.65)	2987 (1 study)	⊕⊕⊕⊖ Moderate ¹	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio; **ST:** superficial thrombophlebitis; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Evidence downgraded one level for imprecision due to a low number of events.

Summary of findings 2. Prophylactic LMWH versus placebo for superficial thrombophlebitis of the leg

Prophylactic LMWH versus placebo for superficial thrombophlebitis of the leg

Patient or population: people with ST of the leg

Settings: hospitalised and non-hospitalised

Intervention: prophylactic LMWH versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Prophylactic LMWH				
Symptomatic VTE Follow-up: 97 days	45 per 1000	54 per 1000 (17 to 174)	RR 1.22 (0.38 to 3.89)	222 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	-
Major bleeding Follow-up: 97 days	See comment	See comment	Not estimable	222 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	0 episodes of major bleeding
Extension or recurrence (or both) of ST Follow-up: 97 days	330 per 1000	145 per 1000 (86 to 244)	RR 0.44 (0.26 to 0.74)	222 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	-
Mortality	See comment	See comment	See comment	-	See comment	Data not available
Minor bleeding	See comment	See comment	See comment	-	See comment	Data not available

Adverse effects of treatment	See comment	See comment	See comment	-	See comment	Data not available
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **ST:** superficial thrombophlebitis; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Evidence downgraded one level due to unclear random sequence generation and incomplete outcome data.

²Evidence downgraded one level for imprecision due to a low number of events.

Summary of findings 3. Therapeutic LMWH versus placebo for superficial thrombophlebitis of the leg

Therapeutic LMWH versus placebo for superficial thrombophlebitis of the leg

Patient or population: people with ST of the leg

Settings: hospitalised and non-hospitalised

Intervention: therapeutic LMWH versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Therapeutic LMWH				
Symptomatic VTE Follow-up: 97 days	45 per 1000	38 per 1000 (10 to 137)	RR 0.85 (0.23 to 3.06)	218 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	-
Major bleeding Follow-up: 97 days	See comment	See comment	Not estimable	218 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	No episodes of major bleeding
Extension or recurrence (or both) of ST Follow-up: 97 days	330 per 1000	152 per 1000 (89 to 254)	RR 0.46 (0.27 to 0.77)	218 (1 study)	⊕⊕⊕⊖ Low ^{1,2}	-

Mortality	See comment	See comment	See comment	-	See comment	Data not available
Minor bleeding	See comment	See comment	See comment	-	See comment	Data not available
Adverse effects of treatment	See comment	See comment	See comment	-	See comment	Data not available

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **ST:** superficial thrombophlebitis; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Evidence downgraded one level due to an unclear random sequence generation and incomplete outcome data.

²Evidence downgraded one level for imprecision due to a low number of events.

Summary of findings 4. NSAIDs versus placebo for superficial thrombophlebitis of the leg

NSAIDs versus placebo for superficial thrombophlebitis of the leg

Patient or population: people with superficial thrombophlebitis of the leg

Settings: hospitalised and non-hospitalised

Intervention: NSAIDs versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	NSAIDs				
Symptomatic VTE Follow-up: 97 days	45 per 1000	41 per 1000 (11 to 146)	RR 0.91 (0.25 to 3.28)	211 (1 study)	⊕⊕○○ Low ^{1,2}	-
Major bleeding Follow-up: 97 days	See comment	See comment	Not estimable	211 (1 study)	⊕⊕○○ Low ^{1,2}	0 episodes of major bleeding

Extension or recurrence (or both) of ST Follow-up: 97 days	330 per 1000	152 per 1000 (89 to 258)	RR 0.46 (0.27 to 0.78)	211 (1 study)	⊕⊕○○ Low ^{1,2}	-
Mortality	See comment	See comment	See comment	-	See comment	Data not available
Minor bleeding	See comment	See comment	See comment	-	See comment	Data not available
Adverse effects of treatment	See comment	See comment	See comment	-	See comment	Data not available

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **NSAIDs:** non-steroidal anti-inflammatory drugs; **RR:** risk ratio; **ST:** superficial thrombophlebitis; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Evidence downgraded one level due to an unclear random sequence generation and incomplete outcome data.

²Evidence downgraded one level for imprecision due to a low number of events.

BACKGROUND

Description of the condition

The term superficial thrombophlebitis (ST), also known as superficial venous thrombosis, refers to a pathological state characterised by an inflammatory-thrombotic process in a superficial vein. Distinctive clinical findings include pain and a reddened, warm, tender cord extending along the vein. The surrounding area may show signs of erythema (reddening of the skin) and oedema (swelling of the tissue). ST is a relatively common disease and, although its incidence has never been properly determined, it is estimated to be higher than that of deep vein thrombosis (DVT), which is about 1 per 1000 cases (De Weese 1991; Nordstrom 1992). In one community-based study conducted in a population of 265,687 adults in France, the annual diagnosis rate of symptomatic, confirmed ST was 0.64% (95% confidence interval (CI) 0.55% to 0.74%) (Frappé 2014).

While the majority of ST occurs in varicose veins, additional predisposing risk factors similar to those for venous thromboembolism (VTE) include immobilisation, trauma, postoperative states, pregnancy, puerperium (the period immediately following childbirth), active malignancy, autoimmune diseases, use of oral contraceptive pills or hormonal replacement therapy, advanced age, obesity, and a history of previous VTE (Barrelier 1993; Bergqvist 1986; Chengelis 1996; de Moerloose 1998; Lutter 1991; Samlaska 1990a). Furthermore, the presence of inherited thrombophilia (a disorder where there is a tendency for thrombosis to occur, for example factor V Leiden, the prothrombin 20210A mutation, and deficiencies of the natural anticoagulant proteins C and S) in ST suggests a similar pathophysiology as VTE (de Moerloose 1998; Hanson 1998; Martinelli 1999; Samlaska 1990a; Samlaska 1990b). Traditionally, ST has been considered a relatively benign disease, but several studies have described an association between ST and VTE (Bergqvist 1986; Blumenberg 1998; Bounameaux 1997; Chengelis 1996; Jorgensen 1993; Krunes 1999; Lutter 1991; Quenet 2003; Unno 2002; Verlato 1999). In people with a diagnosis of ST, 6% to 44% have an associated (or develop) DVT, 20% to 33% have asymptomatic pulmonary embolism (PE), and 2% to 13% have symptomatic PE (Bergqvist 1986; Blumenberg 1998; Bounameaux 1997; Chengelis 1996; Frappé 2014; Jorgensen 1993; Krunes 1999; Lutter 1991; Plate 1985; Quenet 2003; Skillman 1990; Unno 2002; Verlato 1999). ST located in the saphenous main trunk seems to have the strongest association with VTE (Bergqvist 1986; Blumenberg 1998; Chengelis 1996; Jorgensen 1993; Lutter 1991; Quenet 2003; Unno 2002; Verlato 1999). The variations in estimates reported in the literature are probably due to the retrospective design of most studies, the small number of participants included, and the fact that ST was often diagnosed in vascular laboratories where people were referred for suspected DVT. In one cross-sectional and prospective epidemiological cohort study, ST at diagnosis was associated with VTE in 25% of the cases (Decousus 2010a). During a three-month follow-up, 10% of people with ST developed thromboembolic complications despite 90% having received anticoagulant drugs, and about 98% had used elastic compression stockings. In one nationwide population-based cohort study of 10,973 people with a first diagnosis of ST, the incidence of VTE in the first three months after ST diagnosis was 3.4%, which was estimated to be over 70 times higher compared to the general population without ST (Cannegieter 2015).

Description of the intervention

There is no consensus on the optimal treatment of ST in clinical practice as suggested by a survey in 2011 among practitioners mostly from North America showing a large variability in the management of ST (Dua 2014). Several therapies have been proposed in the literature, including surgery (ligation or stripping of the affected veins), elastic stockings, non-steroidal anti-inflammatory drugs (NSAIDs) that aim to reduce pain and inflammation, and several anticoagulant agents. It is unclear whether different locations of ST may influence the choice of treatment. The thrombus location in trunks of either the great saphenous vein (saphena magna) or small saphenous vein (saphena parva) may have the highest risk of extension into the deep vein system and thus could require an aggressive form of treatment, whereas other locations may be associated with a lower risk of extension and thus may warrant a less aggressive approach. Validated risk stratification tools based on ST location and patient characteristics are currently unavailable.

Why it is important to do this review

While the estimates of VTE prevalence in people with ST vary, management of ST should consider the prevention of this scarring complication beyond the mere resolution of local symptoms (Cannegieter 2015; Decousus 2010a; Wichers 2005). Conservative management, mainly focusing on the painful symptoms of disease, might therefore be insufficient. While provision of adequate treatment for ST may help prevent (fatal) VTE, the efficacy of the intervention needs to be balanced against the potential associated risks, such as (major) bleeding events with anticoagulants.

OBJECTIVES

To assess the efficacy and safety of topical, medical, and surgical treatments for ST of the leg in improving local symptoms and decreasing thromboembolic complications.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) evaluating topical, medical, and surgical treatments for ST of the legs.

Types of participants

Hospitalised and non-hospitalised people with a diagnosis of ST of the lower extremities based on signs and symptoms of ST (e.g. pain, tenderness, induration (hardening of the tissue), or erythema (redness of the skin)) in a superficial vein, and objective diagnosis of the thrombus in the superficial vein by means of compression ultrasonography that excludes any concomitant DVT.

Types of interventions

Interventions included any treatment to relieve the symptoms and signs or to prevent complications of ST, such as topical treatments, compression stockings, compression bandages, leg elevation, medical treatments (e.g. NSAIDs, anticoagulants such as fondaparinux, low molecular weight heparin (LMWH) or the oral direct inhibitors of factor Xa or thrombin), and surgical intervention (e.g. ligation, vein stripping, crossectomy). Each treatment could

be compared with another form of treatment, placebo, or no intervention. Combinations of therapies could be used.

Types of outcome measures

We included RCTs assessing any of the following outcome measures for any of the reviewed interventions.

Primary outcomes

Primary efficacy outcome:

- symptomatic VTE (i.e. the combined of symptomatic PE and symptomatic DVT).

Primary safety outcome:

- major bleeding.

The presence of PE or DVT had to be confirmed by an objective test, namely pulmonary angiography, ventilation/perfusion lung scan, or spiral computed tomography for PE; and ultrasonography, venography, or plethysmography for DVT.

Secondary outcomes

The secondary outcomes considered for the review were:

- symptomatic PE;
- symptomatic DVT or the progression of ST into DVT;
- extension (symptomatic and asymptomatic) of ST;
- recurrence (symptomatic and asymptomatic) of ST;
- symptoms (e.g. pain);
- signs (e.g. induration and erythema);
- quality of life (assessed by means of disease-specific and non-specific questionnaires);
- mortality;
- adverse effects of treatment (e.g. minor bleeding, thrombocytopenia (reduced platelet count), allergic reactions, or surgery complications);
- arterial thromboembolic events.

Search methods for identification of studies

We searched for RCTs comparing any treatment versus placebo or another treatment in people with ST of the legs. There was no restriction on language.

Electronic searches

For this update, the Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- Cochrane Vascular Specialised Register (March 2017);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) via the Cochrane Register of Studies Online.

See [Appendix 1](#) for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL, and AMED, and through handsearching of relevant journals. The full list of the databases, journals, and conference proceedings that have been searched, as

well as the search strategies used, are described in the [Specialised Register](#) section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trials registries for details of ongoing and unpublished studies in March 2017:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- ISRCTN Register (www.isrctn.com/).

See [Appendix 2](#).

Searching other resources

We searched reference lists of relevant papers and conference proceedings of the International Society for Thrombosis and Hemostasis (2003 to 2016) and American Society of Hematology (2004 to 2014), and we attempted to contact known experts in the field.

Data collection and analysis

Selection of studies

Two authors (MDN and IMW) independently reviewed titles and abstracts identified from the database searches to determine whether the inclusion criteria were satisfied. Two authors (MDN and IMW) independently assessed trials for inclusion in the review, and resolved any disagreements through discussion or involvement of a third author (SM). We independently reviewed the full text of identified articles, including those where there was disagreement in the initial title or abstract scanning stage, to ensure that the inclusion criteria were met. We obtained hard copies of the full text of studies that fulfilled the selection criteria. We were not blinded to the journal, institution, or results of the study. Titles and abstracts of non-English articles were translated into English and assessed for inclusion. We documented reasons for excluding studies and resolved disagreements by consensus. One author (MDN) scanned conference proceedings, identified articles from other sources (experts or reference lists), and contacted trialists for further information if required.

Data extraction and management

Two authors (MDN and IMW) independently extracted the data from the included studies using an agreed format. We resolved any disagreements by consensus and, if necessary, by the involvement of the third author (SM). For any study published twice, we extracted the data from the more complete study. Collected information included methodological quality, characteristics of participants, type of intervention and control, and outcomes.

Assessment of risk of bias in included studies

Two authors independently assessed randomisation, blinding, and adequacy of analyses ([Juni 2001](#)). We resolved disagreements by consensus.

Two components of randomisation were assessed: generation of allocation sequences and concealment of allocation. Generation of allocation sequences was considered adequate if it resulted in an unpredictable allocation schedule. Mechanisms considered adequate included random-number tables, computer-generated

random numbers, minimisation, coin tossing, shuffling cards, and drawing lots. Trials using an unpredictable allocation sequence were considered randomised. Trials using potentially predictable allocation mechanisms, such as alternation or the allocation of participants according to date of birth, were considered quasi-randomised.

Concealment of allocation was considered adequate if participants and investigators responsible for participants selection were unable to predict, before allocation, which treatment was next. Methods considered adequate included central randomisation; pharmacy-controlled randomisation using identical prenumbered containers; and sequentially numbered, sealed, opaque envelopes.

Blinding of participants and therapists was considered adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used. Assessors were considered blinded if this was explicitly mentioned by the investigators.

Analyses were considered adequate if all randomised participants were included in the analysis according to the intention-to-treat (ITT) principle. The item 'free of selective reporting' was classified as at 'low risk of bias' if we had both the protocol and the full report of a given study, where the full report presented results for all outcomes listed in the protocol. We classified a study as at 'high risk of bias' if a report did not present data on all outcomes reported in either the protocol or the methods section. The risk of bias item 'free of other bias' was not considered in this review. We assessed the reporting of primary outcomes and sample size calculations.

Data synthesis

Prior to obtaining the global effect estimators (a balanced mean of the effect in different trials), we planned to evaluate the heterogeneity of treatment effects between trials using the I^2 statistic (Higgins 2003), which describes the percentage of total variation across trials that is attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% may be interpreted as low, moderate, and high between-trial heterogeneity, although the interpretation of the I^2 statistic depends on the size and number of trials included (Rücker 2008). In the presence of no or low heterogeneity, we planned to use the fixed-effect model (Mantel-

Haenszel method) and the random-effects model to pool and analyse summary effect sizes. Where possible, we presented results as summary risk ratios (RR) or hazard ratios (HRs) for dichotomous variables and mean differences (MD) for all continuous variables. We determined the 95% CI for each estimate. The unit of analysis was the number of participants with the outcome of interest. Where possible, we analysed the results by ITT, including every individual in the randomly assigned treatment group regardless of whether they completed the treatment or withdrew from the trial.

We planned to evaluate publication bias and other biases related to small study size using funnel plots, plotting effect sizes on the vertical axis against their standard errors on the horizontal axis. We planned to assess asymmetry using the asymmetry coefficient: the difference in effect size per unit increase in standard error (Sterne 2001), which is mainly a surrogate for sample size. Symmetry would be expected in the absence of any bias related to small study size.

We used Review Manager 5 for data analysis (RevMan 2014).

'Summary of findings' tables

We presented the main findings of the review concerning the quality of evidence and the magnitude of treatment effects in the 'Summary of findings' tables, according to the GRADE principles described by Higgins 2011 and Guyatt 2008. We used GRADEproGDT software (GRADEproGDT 2015) to create the tables. We included the primary efficacy and safety outcomes of the review as well as the major secondary outcomes (i.e. extension and recurrence of ST, minor bleeding, adverse effects of treatment, and mortality). We focused on the active treatments fondaparinux, LMWH, and NSAIDs with placebo as comparator and at least one primary outcome comparison.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of ongoing studies](#) tables.

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.

There were three new included studies ([Beyer-Westendorf 2017](#); [Boehler 2014](#); [Spirkoska 2015](#)).

Included studies

Three additional studies were included in this third update ([Beyer-Westendorf 2017](#); [Boehler 2014](#); [Spirkoska 2015](#)), giving a total of

33 studies involving 7296 participants (Andreozzi 1996; Anonymous 1970; Archer 1977; Belcaro 1989; Belcaro 1990; Belcaro 1999; Belcaro 2011; Beyer-Westendorf 2017; Boehler 2014; Cosmi 2012; Decousus 2010b; De Sanctis 2001; Ferrari 1992; Gorski 2005; Holzgreve 1989; Incandela 2001; Katzenschlager 2003; Koshkin 2001; Kuhlwein 1985; Lozano 2003; Marchiori 2002; Marshall 2001; Messa 1997; Nocker 1991; Nusser 1991; Pinto 1992; Rathbun 2012; Spirkoska 2015; Stenox Group 2003; Titon 1994; Uncu 2009; Vesalio Group 2005; Winter 1986). Nine studies reported data for 50 participants or fewer, 13 trials for 50 to 100 participants, and 11 studies for 100 participants or more.

Interventions and comparisons varied greatly among the studies. Nine trials included a topical treatment group (Belcaro 2011; De Sanctis 2001; Gorski 2005; Holzgreve 1989; Incandela 2001; Katzenschlager 2003; Nocker 1991; Pinto 1992; Winter 1986); three used a surgical treatment group (Belcaro 1989; Belcaro 1999; Lozano 2003); 14 used LMWH (Belcaro 1989; Belcaro 1990; Belcaro 1999; Cosmi 2012; Gorski 2005; Katzenschlager 2003; Lozano 2003; Marchiori 2002; Rathbun 2012; Spirkoska 2015; Stenox Group 2003; Titon 1994; Uncu 2009; Vesalio Group 2005); six used NSAIDs (Anonymous 1970; Ferrari 1992; Nusser 1991; Rathbun 2012; Stenox Group 2003; Titon 1994); two used fondaparinux (Beyer-Westendorf 2017; Decousus 2010b); one used rivaroxaban (Beyer-Westendorf 2017), and nine studies used another oral (Archer 1977; Belcaro 1989; Belcaro 1999; Koshkin 2001; Kuhlwein 1985; Messa 1997), intramuscular (Andreozzi 1996), intravenous (Marshall 2001), or non-pharmacological (Boehler 2014) treatment.

Excluded studies

Two additional studies were excluded in this update (Ng 2010; Supe 2013) and one study which had previously been in the [Studies](#)

[awaiting classification](#) section (Bijuan 2003) was also excluded making a total of 37 excluded studies. The reasons for exclusion are listed in the [Characteristics of excluded studies](#) table. Twenty-one studies included a mixed population and it was not possible to extract data separately for ST (Allegra 1981; Annoni 1991; Argentero 1983; Bagliani 1983; Becherucci 2000; Bergqvist 1990; Bracale 1996; Bruni 1979; Della Marchina 1989; Luttichau 1989; Mari 1982; Marsala 1985; Mauro 1992; Paciaroni 1982; Porters 1981; Pozza 1980; Seccia 1989; Seghezzi 1972; Seligman 1969; Stolle 1986; Tomamichel 1983). In one study it was not possible to extract outcome data separately for the two study treatment groups (Agus 1993). Four studies included people without a diagnosis of ST of the legs (Bernicot 1980; Gandhi 1984; Resta 1967; van Cauwenberge 1972), and two studies included people with DVT (Di Perri 1986; Rea 1981). In one study, it was unclear whether the study was randomised or not (Giorgetti 1990). Six studies included people with ST of the arm (Gouping 2003; Mehta 1975; Ng 2010; Rozsos 1994; Supe 2013; van der Knaap 1988), and in one study, the evaluated outcomes were not among those considered in the present review (Ibanez-Bermudez 1996). For one study, we were unable to retrieve sufficient information to judge eligibility fully (Bijuan 2003).

Ongoing studies

One study is still ongoing (Rabe 2009). See [Characteristics of ongoing studies](#) table.

Risk of bias in included studies

Details of the methodological quality for each trial are reported in the [Characteristics of included studies](#) table. A risk of bias summary is presented in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Andreozzi 1996	?	?	-	?	+
Anonymous 1970	?	?	?	-	-
Archer 1977	?	?	?	-	+
Belcaro 1989	?	?	-	-	+
Belcaro 1990	?	?	-	?	+
Belcaro 1999	?	?	-	-	+
Belcaro 2011	+	+	-	-	-
Beyer-Westendorf 2017	+	+	-	+	+
Boehler 2014	?	?	-	-	+
Cosmi 2012	+	+	+	-	+
Decousus 2010b	+	+	+	+	+
De Sanctis 2001	?	?	+	+	+
Ferrari 1992	?	?	?	-	+
Gorski 2005	+	?	-	-	+
Holzgrevé 1989	?	?	-	-	+
Incandela 2001	?	?	+	?	+
Katzenschlager 2003	+	?	-	-	+
Koshkin 2001	?	?	?	?	+
Kuhlwein 1985	?	?	?	+	+
Lozano 2003	?	?	-	-	-
Marchiori 2002	+	?	?	+	+
Marshall 2001	+	+	+	-	+

Figure 2. (Continued)

Marshall 2001	+	+	+	-	+
Messa 1997	+	?	-	+	+
Nocker 1991	?	?	?	+	+
Nusser 1991	?	?	+	?	+
Pinto 1992	?	?	+	?	+
Rathbun 2012	+	+	+	?	+
Spirkoska 2015	+	+	?	-	-
Stenox Group 2003	?	+	+	-	+
Titon 1994	?	?	-	-	+
Uncu 2009	-	?	-	?	-
Vesalio Group 2005	+	?	+	+	+
Winter 1986	+	?	?	?	?

Allocation

Thirteen studies adequately generated the randomisation sequence (Belcaro 2011; Beyer-Westendorf 2017; Cosmi 2012; Decousus 2010b; Gorski 2005; Katzenschlager 2003; Marchiori 2002; Marshall 2001; Messa 1997; Rathbun 2012; Spirkoska 2015; Vesalio Group 2005; Winter 1986), one was not adequate (Uncu 2009), and the remaining 18 studies were unclear. Eighteen studies adequately concealed allocation (Belcaro 2011; Beyer-Westendorf 2017; Cosmi 2012; Decousus 2010b; Marshall 2001; Rathbun 2012; Spirkoska 2015; Stenox Group 2003), and the remaining 25 studies were unclear.

Blinding

Ten studies had a double-blinded design (Cosmi 2012; Decousus 2010b; De Sanctis 2001; Incandela 2001; Marshall 2001; Nusser 1991; Pinto 1992; Rathbun 2012; Stenox Group 2003; Vesalio Group 2005), and in nine studies it was unclear whether blinding was attempted (Anonymous 1970; Archer 1977; Ferrari 1992; Koshkin 2001; Kuhlwein 1985; Marchiori 2002; Nocker 1991; Spirkoska 2015; Winter 1986). The remaining 14 studies did not attempt to blind the assessment of the outcomes or did not report whether blinding was used.

Incomplete outcome data

Seven studies performed the analysis according to the ITT principle (Beyer-Westendorf 2017; Decousus 2010b; De Sanctis 2001; Kuhlwein 1985; Marchiori 2002; Messa 1997; Nocker 1991; Vesalio Group 2005); in nine this was unclear, while in the remaining studies the percentage of participants randomised and subsequently excluded from the analysis ranged from 2% to 33% (Anonymous 1970; Archer 1977; Belcaro 1989; Belcaro 1999; Belcaro 2011; Boehler 2014; Cosmi 2012; Ferrari 1992; Gorski 2005; Holzgreve 1989; Katzenschlager 2003; Lozano 2003; Marshall 2001; Spirkoska 2015; Stenox Group 2003; Titon 1994). In Beyer-Westendorf 2017 the primary analysis was originally planned as ITT

analysis, but later modified into a per-protocol analysis. Although 7.6% (36/471) participants randomised were excluded from the primary analysis authors report results also according to the ITT principle.

Selective reporting

Most studies were free of selective reporting except Anonymous 1970; Belcaro 2011; Lozano 2003; Spirkoska 2015; and Uncu 2009 (all high risk), which did not provide data on some of the specified outcomes and Winter 1986 (unclear risk), which was reported as an abstract only and did not prespecify outcomes.

Effects of interventions

See: **Summary of findings for the main comparison** Fondaparinux compared to placebo for superficial thrombophlebitis of the leg; **Summary of findings 2** Prophylactic LMWH versus placebo for superficial thrombophlebitis of the leg; **Summary of findings 3** Therapeutic LMWH versus placebo for superficial thrombophlebitis of the leg; **Summary of findings 4** NSAIDs versus placebo for superficial thrombophlebitis of the leg

None of the studies evaluated similar treatments on the same study outcomes. Treatment included fondaparinux, rivaroxaban, LMWH, unfractionated heparin (UFH), NSAIDs, topical treatment, oral treatment, intramuscular treatment, and intravenous treatment to surgery.

Fondaparinux

The CALISTO study, a large double-blinded, placebo-controlled RCT, evaluated a prophylactic dose (2.5 mg subcutaneously (sc) once daily) of fondaparinux given for 45 days (Decousus 2010b). The primary efficacy outcome of this RCT (i.e. composite of death from any cause, symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of ST up to day 47) was reduced by 85% by

fondaparinux (RR 0.15, 95% CI 0.08 to 0.26) with a number needed to treat for an additional beneficial outcome (NNTB) of 20. The incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group compared with the placebo group except for the incidence of PE and of death, which did not differ significantly between the two groups (Analysis 1.1; Analysis 1.6). The risk of the composite of symptomatic DVT or PE was reduced by 85% with fondaparinux compared with placebo (RR 0.15, 95% CI 0.04 to 0.50) with a NNTB of 88. Fondaparinux was associated with lower rates of extension (RR 0.08, 95% CI 0.03 to 0.22) and recurrence of ST (RR 0.21, 95% CI 0.08 to 0.54). By day 47, major bleeding had occurred in one participant (0.1%) in each group (RR 0.99, 95% CI 0.06 to 15.86; $P = 1.00$). The rate of clinically relevant non-major, minor, and total bleeding; arterial thromboembolic complications; and adverse effects of treatment did not differ significantly between the two groups.

In the SURPRISE study, 472 people with ST and one or more risk factors for thromboembolic complications (older than 65 years, male sex, previous ST or DVT or PE, active cancer or history of cancer, autoimmune disease, or involvement of non-varicose veins) were randomised to fondaparinux (2.5 mg sc once daily) or the oral direct factor Xa inhibitor rivaroxaban (10 mg once daily) (Beyer-Westendorf 2017). In the per-protocol analysis, the incidence of the primary efficacy outcome (i.e. composite of symptomatic DVT or PE, progression or recurrence of ST, and all-cause mortality at 45 days) was comparable in the rivaroxaban and fondaparinux groups at day 45 (3% with rivaroxaban versus 2% with fondaparinux; HR 1.9, 95% CI 0.6 to 6.4) and at 90 days, (7% with rivaroxaban versus 7% with fondaparinux; HR 1.1, 95% CI 0.5 to 2.2).

There were similar results when the analysis was performed according to the ITT principle. Fondaparinux was associated with a non-statistically significant reduction of symptomatic VTE, DVT, recurrence of ST, mortality, clinically relevant non-major bleeding, serious adverse events, or adverse effects of treatment compared with rivaroxaban (Analysis 2.2; Analysis 2.3; Analysis 2.5; Analysis 2.6; Analysis 2.8; Analysis 2.10; Analysis 2.11). There were no cases of PE, extension of ST or major bleeding in either treatment arm.

Low molecular weight heparin and unfractionated heparin

Fourteen studies included a LMWH group (Belcaro 1989; Belcaro 1990; Belcaro 1999; Cosmi 2012; Gorski 2005; Katzenschlager 2003; Lozano 2003; Marchiori 2002; Rathbun 2012; Spirkoska 2015; Stenox Group 2003; Titon 1994; Uncu 2009; Vesalio Group 2005).

Although not statistically significant, the incidence of VTE tended to be lower with both prophylactic and therapeutic LMWH compared with placebo shortly after treatment (prophylactic: RR 0.25, 95% CI 0.03 to 2.24; therapeutic: RR 0.26, 95% CI 0.03 to 2.33). However, at the end of the three-month follow-up, this difference was even less evident suggesting a catch-up phenomenon (Analysis 3.2; Analysis 4.2) (Stenox Group 2003). Prophylactic and therapeutic LMWH given for eight to 12 days significantly reduced ST extension or recurrence, or both, compared with placebo (prophylactic: RR 0.44, 95% CI 0.26 to 0.74; therapeutic: RR 0.46, 95% CI 0.27 to 0.77). There were no episodes of major bleeding or heparin-induced thrombocytopenia (HIT) in any treatment group (Stenox Group 2003).

Combined therapy with LMWH plus elastic compression stockings seemed to reduce the incidence of VTE and ST extension or

recurrence, or both, compared with elastic stockings alone (VTE: RR 0.08, 95% CI 0.00 to 1.38; ST extension or recurrence, or both: RR 0.08, 95% CI 0.01 to 0.59), although the former difference was not statistically significant (Belcaro 1999). This study did not provide data on safety outcomes.

Two studies randomised participants to topical treatment with heparin spray gel or LMWH (Gorski 2005; Katzenschlager 2003). There was a non-significant decrease in DVT with LMWH (RR 0.30, 95% CI 0.03 to 2.70) and relief of local symptoms of ST was similar between both treatments at 21 days (Gorski 2005).

One study evaluated LMWH versus surgical treatment (saphenofemoral disconnection) (Lozano 2003). There was a comparable reduction of VTE events and a similar safety profile in the two study groups. There were numerically more cases of ST extension or recurrence with LMWH, although numbers were low and differences were not statistically significant (RR 3.00, 95% CI 0.33 to 27.23).

Three studies evaluated LMWH versus NSAIDs (Rathbun 2012; Stenox Group 2003; Titon 1994). Compared to NSAIDs, both fixed-dose LMWH and weight-adjusted LMWH seemed to have a similar effect on VTE (RR 0.93, 95% CI 0.24 to 3.63) and ST recurrence (RR 1.01, 95% CI 0.58 to 1.78). In the study by Rathbun 2012, there was one case of ST progression into the posterior tibial veins and one symptomatic PE, both in the LMWH group. Rathbun 2012 was not pooled with the other two studies for the outcome VTE since the administration of therapeutic LMWH in any person with thrombus progression during follow-up could have introduced significant confounding. In Stenox Group 2003, which used placebo as a control group, an indirect comparison between prophylactic LMWH and NSAIDs suggested a non-statistically significant reduction in VTE at the end of treatment (RR 0.45, 95% CI 0.04 to 4.89). There were no major bleeding events or HIT in either group. Rathbun 2012 reported two episodes of cutaneous rash with LMWH. In addition, there was a significant reduction in pain with both LMWH and NSAIDs with no differences between the groups.

One study compared LMWH alone versus LMWH combined with the anti-inflammatory agent acemetacin (Uncu 2009). There were no cases of VTE, extension of ST, or major bleeding in either group. The effects on signs and symptoms of ST were not statistically different (Analysis 14.4; Analysis 14.5; Analysis 14.6; Analysis 14.7).

Three studies compared different regimens of LMWH head-to-head but without using a placebo or inactive control group (Cosmi 2012; Spirkoska 2015; Vesalio Group 2005). In Cosmi 2012 (the STEFLUX study), the incidence of symptomatic VTE at the end of treatment and at the three-month follow-up was not different in the 30-day intermediate-dose LMWH and 30-day prophylactic dose LMWH groups (Analysis 5.1; Analysis 5.2), and it was lower in the 30-day intermediate-dose LMWH compared with the 10-day intermediate-dose LMWH (VTE end-of-treatment: 0.46% with 30-day intermediate-dose LMWH versus 4.72% with 10-day intermediate-dose LMWH, RR 0.10, 95% CI 0.01 to 0.75; VTE 3-month follow-up: 1.82% with 30-day intermediate-dose LMWH versus 5.19% with 10-day intermediate-dose LMWH, RR 0.35, 95% CI 0.11 to 1.09; Analysis 7.1; Analysis 7.2). At the three-month follow-up, symptomatic PE had occurred in none of the participants of the 30-day intermediate-dose group and in one participant of both the 10-day intermediate-dose and 30-day prophylactic-dose LMWH groups. The incidence of symptomatic DVT did not differ

between the three groups (Analysis 5.4; Analysis 6.4; Analysis 7.4). ST extension at three months was significantly reduced by the 30-day intermediate-dose LMWH in comparison to both the 30-day prophylactic (2.28% with 30-day intermediate-dose versus 8.29% with 30-day prophylactic dose LMWH; RR 0.28, 95% CI 0.10 to 0.73) and 10-day intermediate dose LMWH (10.38%, RR 0.22, 95% CI 0.08 to 0.57), while recurrence of ST was similar in the 30-day intermediate-dose LMWH and the other two groups (Analysis 5.6; Analysis 7.6). There were no cases of major bleeding or HIT. The intensity of local symptoms evaluated by visual analogue scales (VAS) was comparable in the 30-day intermediate-dose, 10-day intermediate-dose, and the 30-day prophylactic-dose LMWH at the start of treatment (5.0 with 30-day intermediate-dose, 5.1 with 10-day intermediate-dose, 5.1 with 30-day prophylactic-dose; $P = 0.97$) as well as at the end of treatment (0.7 with 30-day intermediate-dose, 0.6 with 10-day intermediate-dose, 0.8 with 30-day prophylactic-dose; $P = 0.10$) and at three months (0.2 with 30-day intermediate-dose, 0.3 with 10-day intermediate-dose, 0.4 with 30-day prophylactic-dose; $P = 0.47$). Allergic reactions occurred in 0.4% with 30-day intermediate-dose, 1.4% with 10-day intermediate-dose, and 0% with 30-day prophylactic-dose.

In Spirkoska 2015, one participant in the intermediate-dose LMWH group developed a symptomatic PE versus none in the prophylactic-dose LMWH group. Asymptomatic ST progression into DVT occurred in one participant in each group. There were no major bleeding events. The authors reported a regression of the thrombus at the end of the study period in 66% of participants receiving the prophylactic-dose LMWH compared to 80% in the intermediate-dose LMWH and a complete thrombus resolution with recanalisation in three participants (9.7%) in the prophylactic-dose LMWH and six (19.4%) participants in the intermediate-dose LMWH. These differences were not statistically significant.

In the Vesalio Group 2005, one month of weight-adjusted full therapeutic dose of LMWH or fixed prophylactic-dose LMWH led to a similar reduction in ST extension or recurrence, or VTE (RR 1.20, 95% CI 0.42 to 3.40) over a three-month follow-up. In the prophylactic-dose LMWH group most of the VTE events (77%) occurred while participants were still on treatment, whereas only 33% of participants on therapeutic-dose LMWH developed VTE during LMWH administration. This advantage was lost after drug discontinuation with no difference at the end of the study period. There was no major bleeding or HIT during the study. Local symptoms and signs regressed faster with therapeutic dose LMWH although the difference was not statistically significant.

Two studies used sc UFH at prophylactic doses as the comparator treatment (Belcaro 1999; Marchiori 2002). Relative to elastic stockings alone, prophylactic sc UFH plus elastic stockings was associated with a statistically non-significant lower VTE rate (RR 0.08, 95% CI 0.00 to 1.47) and a 83% reduction in ST extension or recurrence (RR 0.17, 95% CI 0.04 to 0.72) (Belcaro 1999). One study compared high- versus low-dose sc UFH. There was a non-significant 83% reduction in VTE (RR 0.17, 95% CI 0.02 to 1.30) and a 27% (RR 0.73, 95% CI 0.34 to 1.55) reduced rate of ST extension or recurrence among participants treated with high-dose UFH (Marchiori 2002). There were no episodes of major bleeding or HIT in either study group.

Two studies evaluated sc heparin calcium (Belcaro 1989; Belcaro 1990). The combination of elastic stockings plus heparin calcium did not significantly improve local symptoms and signs compared

with elastic stockings alone. Treatment with heparin calcium was correlated with a faster reduction of the analogue score and the area at maximum temperature than with defibrotide, although the difference was not significant. There were no adverse effects.

Non-steroidal anti-inflammatory drugs

Six studies included an NSAID group (Anonymous 1970; Ferrari 1992; Nusser 1991; Rathbun 2012; Stenox Group 2003; Titon 1994). Of these, two compared NSAIDs with placebo (Anonymous 1970; Stenox Group 2003), three NSAID with LMWH (Rathbun 2012; Stenox Group 2003; Titon 1994), and two randomised participants to two different NSAIDs (Ferrari 1992; Nusser 1991). The trials comparing NSAIDs versus LMWH have been discussed previously (Rathbun 2012; Stenox Group 2003; Titon 1994).

NSAIDs significantly reduced the risk of ST extension or recurrence, or both, by 54% compared with placebo (RR 0.46, 95% CI 0.27 to 0.78) (Stenox Group 2003). However, there were no differences in the incidence of VTE or in the resolution of local symptoms and signs. While there were no major bleeding episodes recorded in any of the NSAID or placebo groups, indomethacin tended to increase the rate of adverse effects compared with placebo (RR 2.60, 95% CI 0.95 to 7.08) (Anonymous 1970).

In one study, oral acemetacin led to a better resolution of the local clinical picture than diclofenac (Nusser 1991). Another trial compared nimesulide with diclofenac sodium (Ferrari 1992). Local symptoms were similarly improved by both treatments. In the group of participants randomised to nimesulide, there was a lower incidence of gastric pain episodes (RR 0.25, 95% CI 0.03 to 2.08) although this difference was not statistically significant (Ferrari 1992).

Topical treatment

Nine studies included a topical treatment group (Belcaro 2011; De Sanctis 2001; Gorski 2005; Holzgreve 1989; Incandela 2001; Katzenschlager 2003; Nocker 1991; Pinto 1992; Winter 1986). The comparison of heparin spray gel versus LMWH has been discussed earlier (see Low molecular weight heparin and unfractionated heparin section; Gorski 2005; Katzenschlager 2003).

Belcaro 2011 randomised participants to three doses of heparin spray gel versus placebo for seven to 14 days. After one week, there was a significant reduction in pain assessed by the VAS with heparin spray gel (-93.13% reduction with heparin spray gel versus -61.35% reduction with placebo; $P < 0.0001$), a lower erythema extension (-92% with heparin spray gel versus -26% with placebo; $P < 0.012$), and thrombus length (-40.81 with heparin spray gel versus -4.22 with placebo; $P < 0.0001$). There were no adverse events or drug-related reactions reported.

One study randomised participants to receive topical methylthioadenosine or placebo (Pinto 1992). Methylthioadenosine was associated with a non-significant reduction in local signs and symptoms relative to placebo.

A significant improvement in the local symptomatology was observed with diclofenac gel (Nocker 1991) and essaven gel (De Sanctis 2001; Incandela 2001) compared with placebo.

Holzgreve 1989 and Winter 1986 compared two different types of gel. Holzgreve 1989 evaluated diclofenac gel versus etofenak

gel and showed a comparable efficacy profile of the two topical medications. [Winter 1986](#) compared diclofenac gel and heparin gel and found a better efficacy with diclofenac gel.

None of the studies evaluating a topical treatment reported data on VTE or ST recurrence.

Surgery

Three studies included a surgical treatment ([Belcaro 1989](#); [Belcaro 1999](#); [Lozano 2003](#)). One study compared surgery (saphenofemoral disconnection) with LMWH (see Low molecular weight heparin and unfractionated heparin section; [Lozano 2003](#)). The remaining two studies compared surgery combined with elastic stockings with elastic stockings alone ([Belcaro 1989](#); [Belcaro 1999](#)).

One trial found that thrombectomy plus elastic stockings with or without venoruton led to an improvement of the local clinical signs and a greater reduction in the number of veins with ST compared with elastic compression bandages alone ([Belcaro 1989](#)). There were no cases of DVT in either group. One trial found that ligation of the vein plus elastic stockings was associated with a non-significant reduction in VTE events (RR 0.33, 95% CI 0.07 to 1.60) and ST recurrence and extension (RR 0.46, 95% CI 0.18 to 1.15) relative to the control treatment ([Belcaro 1999](#)).

Compared with elastic stockings alone, venous stripping plus elastic stockings decreased the risk of ST extension and recurrence (RR 0.09, 95% CI 0.01 to 0.64) and seemed to be associated with a lower, non-significant, incidence of VTE (RR 0.37, 95% CI 0.08 to 1.78) ([Belcaro 1999](#)).

Other

Nine studies evaluated an oral ([Archer 1977](#); [Belcaro 1989](#); [Belcaro 1999](#); [Koshkin 2001](#); [Kuhlwein 1985](#); [Messa 1997](#)), intramuscular ([Andreozzi 1996](#)), intravenous ([Marshall 2001](#)), or non-pharmacological ([Boehler 2014](#)) treatment. [Beyer-Westendorf 2017](#) compared oral rivaroxaban with fondaparinux and has been presented above (see Fondaparinux section).

Compared with placebo, oral vasotonin was associated with a higher proportion of participants who were cured or improved ([Kuhlwein 1985](#)). The criteria to determine the response to study treatment were not described. Vasotonin seemed to be well tolerated, with one case of poor tolerability among participants treated with vasotonin (3%) versus five cases (13%) in the placebo arm (RR 0.20, 95% CI 0.02 to 1.63).

The combination of venoruton, thrombectomy, and elastic stockings versus elastic stockings alone has been discussed above (see Low molecular weight heparin and unfractionated heparin section; [Belcaro 1989](#)). In the same trial, venoruton combined with elastic stockings led to an improvement of local symptoms compared with elastic stockings alone.

One study evaluating oral heparansulphate versus oral sulodexide suggested a greater decrease in local pain, itching, and redness in participants receiving oral heparansulphate than in the group receiving sulodexide ([Messa 1997](#)).

Compared with placebo, oxyphenbutazone reduced local tenderness four-fold and halved the intensity of pain and erythema ([Archer 1977](#)).

One study evaluated oral vitamin K antagonists in combination with elastic stockings, which suggested a non-significant reduction in VTE events (RR 0.08, 95% CI 0.00 to 1.47) and ST extension or recurrence (RR 0.42, 95% CI 0.16 to 1.13) with vitamin K antagonists plus elastic stockings compared with elastic stockings alone ([Belcaro 1999](#)).

Two studies addressed the use of enzyme therapy versus placebo ([Koshkin 2001](#); [Marshall 2001](#)). Enzyme treatment seemed to improve local symptoms although the criteria to evaluate the response to study treatment were not reported.

One trial assessed the efficacy of three doses of desmin ([Andreozzi 1996](#)). There was a better control of local symptoms with higher doses of desmin without any increase in the risk of adverse events.

One study evaluated LMWH plus compression stockings versus LMWH alone ([Boehler 2014](#)). At the three-week follow-up, there was no difference between the two groups with regard to pain intensity (mean difference -0.15 cm, 95% CI -0.95 to 0.65), skin erythema (-6.54 cm², 95% CI -17.94 to 4.86), or quality of life evaluated through the 36-item Short Form (SF-36) Physical score (mean difference 2.92, 95% CI -1.04 to 6.88) and SF-36 Mental score (-2.98, 95% CI -7.30 to 1.34). There was no DVT or HIT.

DISCUSSION

Uncertainty still exists around the optimal treatment of ST of the legs. The therapeutic approach for ST should aim at the resolution or improvement of the local symptoms but also, and even more importantly, at preventing the possible extension of the superficial vein thrombosis into the deep venous system ([Wichers 2005](#)).

This review summarised data from 7296 people with ST of the legs. About half of the participants were included in the CALISTO study, which compared 45 days of fondaparinux versus placebo using a double-blind method ([Decousus 2010b](#)). Fondaparinux reduced the incidence of symptomatic VTE by 85%, ST extension by 92%, and the recurrence of ST by 79%. A total of 88 participants would need to be treated with fondaparinux to prevent one PE or DVT. These benefits were achieved without apparently increasing the risk of bleeding and they were maintained at one-month follow-up after discontinuation of treatment. However, CIs around bleeding estimate were broad and did not exclude a significantly higher risk with the drug. In the SURPRISE study, people with ST and one or more risk factors for thromboembolic complications were randomised to 45 days of fondaparinux or rivaroxaban 10 mg ([Beyer-Westendorf 2017](#)). The results suggested that rivaroxaban was as effective as fondaparinux; however, the study was not powered to prove non-inferiority. In addition, the authors observed a non-statistically significant increase of the primary composite outcome as well as of clinically relevant non-major bleedings in the rivaroxaban group which require further evaluation in appropriately sized studies. In contrast to the CALISTO study, the risk of thromboembolic events seemed to increase after treatment withdrawal at 45 days suggesting that a longer treatment may be required for people at high risk.

Compared with placebo or topical treatments, both NSAIDs and LMWH could help preventing ST extension while effectively controlling local symptoms ([Stenox Group 2003](#); [Titon 1994](#)). When compared with each other, LMWH and NSAIDs seemed to be associated with a similar reduction in the incidence of VTE and

worsening of ST. However, these conclusions need to be taken cautiously due to the methodological drawbacks, the low incidence of VTE, and the sample size of the available studies, which did not have enough power for a direct comparison between LMWH and NSAIDs. Thus, these data remain preliminary and further research is required to determine which treatment works better in terms of VTE prevention, and whether a combination may be more effective. Moreover, the benefits of LMWH and NSAIDs should be balanced against the associated adverse effects such as bleeding and gastric complications. None of the studies reported major bleeding episodes in participants randomised to LMWH. NSAIDs increased the risk of gastric pain three-fold compared with placebo. To date, no study has evaluated NSAIDs versus surgery whereas one trial directly compared LMWH with surgical treatment, showing a comparable efficacy and safety (Lozano 2003). Despite the methodological limitations of this study, the results would suggest that a medical approach with LMWH would be as effective and safe as an invasive surgical treatment.

Cosmi 2012 and Vesalio Group 2005 compared different regimens of LMWH head-to-head. While symptomatic VTE occurred at a similar rate with prophylactic and higher (intermediate or therapeutic) dose LMWH, the higher-dose LMWH seemed to be associated with a significant 70% reduction in ST progression (Cosmi 2012). Furthermore, the findings of Cosmi 2012 suggested that treatment with LMWH should be prolonged for at least 30 days to reduce the incidence of symptomatic VTE, compared to shorter usage of LMWH. However, it should be noted that neither Cosmi 2012 nor Vesalio Group 2005 had a placebo or inactive control group and Cosmi 2012 was prematurely interrupted, which may have led to an overestimation of the differences between the groups.

In the study of Boehler 2014, the addition of compression stockings to prophylactic dose LMWH seemed to carry no additional benefit in terms of clinical improvement.

Preliminary data suggested that high-dose UFH can be effective in the treatment of ST although this needs to be confirmed in larger studies (Marchiori 2002). While not directly evaluated against UFH, fondaparinux and LMWH may still be preferable due to the easier mode of administration and the more predictable response not requiring laboratory monitoring as for UFH.

Most of the studies comparing oral treatment, topical treatment, or surgery did not report VTE, ST progression, adverse events, or treatment adverse effects. In addition, the methodological quality of these studies was often poor, with major study design flaws such as an unclear method of allocation or randomisation, the lack of a placebo as control group, or an unacceptably high dropout rate. All these limitations weaken the clinical applicability of the results and cast doubt about the actual efficacy and safety of these treatments.

Summary of main results

Fondaparinux was associated with a significant lower incidence of VTE, ST extension, or ST recurrence relative to placebo with similar risk of bleeding. Rivaroxaban 10 mg requires further evaluation. As compared to placebo, LMWH and NSAIDs appeared to reduce the extension or recurrence of ST, or both, whereas the available data did not show any significant effect on VTE. The evidence on oral treatments, topical treatment, or surgery was too limited and did not inform clinical practice about the effects of these treatments in terms of VTE.

Quality of the evidence

Our systematic approach to searching, study selection, and data extraction followed that of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The methodological quality of the included studies varied from low to high (see Figure 2). Poor reporting did not allow proper scoring of relevant study design features, such as sequence generation and allocation concealment, in the majority of included studies. Overall, the quality of evidence was very low for most intervention outcomes due to limitations in study design, imprecision of results and single study comparisons. The quality of evidence was low to moderate for outcomes in the two placebo-controlled studies included in this review (Decousus 2010b; Stenox Group 2003). See [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); and [Summary of findings 4](#).

Potential biases in the review process

One limitation of this review is that, despite the relatively large number of comparisons found, only a few studies compared the same treatment on the same study outcomes. The 'no difference' findings on a specific outcome may thus be the result of insufficient power of the analysis to show a difference between treatment groups as well as the absence of a true effect. For similar reasons, it was not possible to conduct subgroup analyses for the primary efficacy outcomes to evaluate the interaction of trial characteristics with treatment effects.

Agreements and disagreements with other studies or reviews

Since our previous systematic review on the prevention of VTE in people with ST of the leg (Wichers 2005), the results of two large RCTs on the efficacy of fondaparinux for the treatment of ST have become available (Beyer-Westendorf 2017; Decousus 2010b). The high methodological quality and the size of the CALISTO study (Decousus 2010b), which alone accounted for half of the overall review population, made it a landmark investigation in the field. The SURPRISE study was the first to compare one of the direct oral factor Xa inhibitors, rivaroxaban, with fondaparinux and to select people with ST based on their underlying risk of thromboembolic events.

AUTHORS' CONCLUSIONS

Implications for practice

Given the available evidence, prophylactic-dose fondaparinux appears to be a valid treatment option in most people with ST. Fondaparinux should be given at a dose of 2.5 mg subcutaneously once daily for 45 days. Final recommendations cannot be drawn for rivaroxaban, low molecular weight heparin (LMWH), unfractionated heparin, or non-steroidal anti-inflammatory drugs (NSAID). Data are still too preliminary to draw firm conclusions on the role of surgery and the topical, oral, and parenteral treatments evaluated this far.

Implications for research

Several questions about the treatment of ST remain unsolved. The role of rivaroxaban and other oral direct factor Xa inhibitors for the management of ST requires further evaluation. As suggested by the results of the SURPRISE study, the efficacy of anticoagulant

treatment may vary according to the presence of underlying risk factors for recurrent thromboembolic events ([Beyer-Westendorf 2017](#)). Individuals at increased risk could benefit of higher intensity or longer anticoagulant treatment. The usefulness, potential healthcare benefits and cost-savings of risk stratification tools needs to be evaluated. Additional studies should assess the costs, effects on quality of life, and the cost-effectiveness of fondaparinux ([Goldman 2010](#)). Large and adequately designed randomised controlled trials would be required to assess the actual role of NSAIDs and LMWH, and how these drugs compare with fondaparinux. Whether topical treatment might add some benefit if given in combination with fondaparinux remains unclear.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Andreozzi 1996

Methods	Multicentre, open RCT.
Participants	56 participants with ST or varicophlebitis of lower limbs; 19 males, 36 females; mean age range 48-52 years. Diagnosis of ST objectively confirmed by Doppler compression ultrasonography. Not reported if the included participants were hospitalised or non-hospitalised.
Interventions	Desmin (Dermatan sulphate) (100 mg bid sc). Desmin (200 mg od im). Desmin (100 mg od sc). Study treatment given for 30 days.
Outcomes	Pain and functional inability, local oedema, palpable thrombophlebitic cord, fever, hyperaemia and cutaneous hyperthermia, adverse events or adverse drug reactions.
Notes	Funding: Alfa Wassermann S.p.A (Bologna, Italy) supplied desmin. Disclosure of potential COI: 2 authors from Alfa Wassermann S.p.A., Bologna, Italy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study "open and multicenter."

Treatment for superficial thrombophlebitis of the leg (Review)

Andreozzi 1996 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants analysed unclear. 1 participant discontinued treatment and was excluded from baseline descriptive table.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section.

Anonymous 1970

Methods	Placebo-controlled, double-blind RCT.
Participants	56 participants with ST of the calf (68%), thigh (16%), both (16%). Not reported if included participants were hospitalised or non-hospitalised. Not reported if diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Indomethacin (50 mg tid). Placebo. Study treatment given for 1 week.
Outcomes	Erythema, spontaneous pain, tenderness, oedema.
Notes	Every participant received tetracyclines (250 mg 4 times daily), paracetamol when required, warm socks (5 participants in indomethacin group, 3 in placebo group). Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "...comparison between indomethacin and inactive placebo..the choice being determined by random selection."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind study. "double-blind comparison;" however, not reported who was blinded and how blinding was attempted.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not clear how many participants of those initially included had full assessment of the study endpoints. From Table 1 in Anonymous 1970 , it was clear that ≥ 1 of the outcomes not all participants were evaluated at longest follow-up.
Selective reporting (reporting bias)	High risk	No data provided for some of the outcomes. Adverse effects reported in the results section but not mentioned in the methods section.

Archer 1977

Methods	Multicentre, double-blind RCT.
Participants	54 non-hospitalised participants with ST; 18 males, 36 females; mean age 55 years. Not reported if the diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Oxyphenbutazone (Tandacote) (100 mg 4 times daily). Placebo (4 times daily). Study treatment given for 7 days.
Outcomes	Pain, erythema, tenderness, length of indurated vein.
Notes	Paracetamol and firm bandaging allowed. Outcome tenderness assessed in 24/26 participants in the oxyphenbutazone group. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "Oxyphenbutazone..and matching placebo were allocated at random."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No clear information provided about blinding. "...none was a satisfactory double-blind controlled study...". "...it was felt that such a study should be undertaken..". It could be a double blinded study, however, blinding is not clearly mentioned in the methods, results or discussion sections. Not reported who was blinded and how blinding was attempted.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant (from the placebo group) excluded postrandomisation (2%). Unclear if all the remaining participants were analysed.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported.

Belcaro 1989

Methods	Open RCT.
Participants	83 participants with ST without DVT on duplex ultrasonography; 36 males, 45 females; mean age 38.9 years (range 27-46 years). Not reported if participants were hospitalised or non-hospitalised.
Interventions	ST + ECB. Heparin calcium (0.5 mg bid sc) + ECB. Venoruton (1000 mg tid) + ECB. Venoruton (1000 mg tid) after ST + ECB.

Treatment for superficial thrombophlebitis of the leg (Review)

Belcaro 1989 (Continued)

ECB alone.

Non-surgical treatment given for 8 weeks.

Outcomes	Area of maximum temperature, pain and tenderness (analogical score), DVT. Not specified if DVTs were symptomatic or asymptomatic.
Notes	<p>6/9 participants excluded postrandomisation underwent surgery of the superficial venous system. DVT verified at 6 weeks by strain-gauge plethysmography.</p> <p>Funding: not reported.</p> <p>Disclosure of potential COI: not reported, no COI forms available.</p> <p>Gianni Belcaro erased from the UK medical register in June 2007 for "misconduct," which seems to have been that he included as coauthors on his papers people who were not involved in the research. The General Medical Council report did not suggest that data were falsified webcache.gmc-uk.org/minutesfiles/3313.HTML.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "patients were randomized in 5 groups of treatment."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No information provided about blinding, but it was likely an open study.
Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants excluded after inclusion in the study (10%): "6 patients underwent surgery of the superficial venous system and 3 failed to follow the prescribed treatments."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Belcaro 1990

Methods	Single-centre RCT.
Participants	40 participants with ST confirmed by colour duplex ultrasonography; 13 males, 27 females; aged 46-48 years. Not reported if participants were hospitalised or non-hospitalised. Angiodynography used to exclude the presence of obstruction and DVT.
Interventions	<p>Defibrotide (first week 400 mg bid; second and third weeks 400 mg od).</p> <p>Low-dose heparin (5000 IU bid sc) for 3 weeks.</p>
Outcomes	Area of maximum temperature, analogue score (redness, local tenderness, inflammation).
Notes	<p>All participants received compression bandages.</p> <p>Funding: not reported.</p>

Belcaro 1990 (Continued)

Disclosure of potential COI: not reported, no COI forms available.

Gianni Belcaro erased from the UK medical register in June 2007 for "misconduct," which seems to have been that he included as coauthors on his papers people who were not involved in the research. The General Medical Council report did not suggest that data were falsified webcache.gmc-uk.org/min-utesfiles/3313.HTML.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "Patients were randomized in two treatment groups."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No information provided about blinding, but it was likely an open study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all included participants were evaluated for study outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Belcaro 1999

Methods	Multicentre, open RCT; 6-month follow-up.
Participants	562 non-hospitalised participants with ST, large varicose veins, and venous incompetence; 181 males, 263 females; mean age range across study groups 53-56 years. Diagnosis of ST objectively confirmed by colour Doppler compression ultrasonography.
Interventions	<p>Surgery (ligation).</p> <p>Surgery (complete stripping).</p> <p>Low-dose sc heparin.</p> <p>LMWH.</p> <p>Coumadin.</p>
Outcomes	DVT and extension of ST after treatment and after 3 and 6 months. Not specified if DVT and extension of ST were symptomatic or asymptomatic.
Notes	<p>All participants received compression bandages. Duration of non-surgical treatments unclear and dose of heparin or coumadin not specified.</p> <p>Funding: not reported.</p> <p>Disclosure of potential COI: not reported, no COI forms available.</p> <p>Gianni Belcaro erased from the UK medical register in June 2007 for "misconduct," which seems to have been that he included as coauthors on his papers people who were not involved in the research.</p>

Belcaro 1999 (Continued)

The General Medical Council report did not suggest that data were falsified webcache.gmc-uk.org/min-utesfiles/3313.HTML.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No information provided about blinding, but it was likely an open study.
Incomplete outcome data (attrition bias) All outcomes	High risk	118 (21%) participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Belcaro 2011

Methods	Single-centre, randomised, placebo-controlled study.
Participants	120 non-hospitalised participants with ST of the legs within 72 hours prior to study inclusion. ST confirmed by colour-Doppler ultrasonography. Mean age 46.3 years (11.51), 26 males, 94 females.
Interventions	Heparin spray gel (Viatromb 2400 IU/g): 4122 IU sodium heparin applied as 3 times 3 spray puffs. Heparin spray gel (Viatromb 2400 IU/g): 5496 IU sodium heparin applied as 3 times 4 spray puffs. Heparin spray gel (Viatromb 2400 IU/g): 6879 IU sodium heparin applied as 3 times 5 spray puffs. Placebo applied as 3 times 5 puffs. Study medication applied for 7-14 days.
Outcomes	Pain reduction (VAS scale and VRS), erythema extension, thrombus size, oedema reduction, adverse events, investigator's and participant's assessment of efficacy.
Notes	Funding: study sponsored by CRO Opera S.r.L., Genoa, Italy. Disclosure of potential COI: authors reported to have no COI. Gianni Belcaro erased from the UK medical register in June 2007 for "misconduct," which seems to have been that he included as coauthors on his papers people who were not involved in the research. The General Medical Council report did not suggest that data were falsified webcache.gmc-uk.org/min-utesfiles/3313.HTML .

Risk of bias

Bias	Authors' judgement	Support for judgement
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Belcaro 2011 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated: "The treatments were allocated according to a randomization list (randomization by blocks)." Block allocation sequences created at random by using numbers generated by a computer program.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation sequence. "Each subject enrolled into the study received the respective lowest randomization number available."
Blinding (performance bias and detection bias) All outcomes	High risk	Single blind: "observer blinded design."
Incomplete outcome data (attrition bias) All outcomes	High risk	14/150 (11.7%) dropped out, 68.3% completed treatment on day 7, 11.7% on day 14, and 8.3% had treatment failure.
Selective reporting (reporting bias)	High risk	Data not reported for all prespecified outcomes. DVT mentioned in methods but not reported in results or discussion.

Beyer-Westendorf 2017

Methods	Open-label, masked endpoint, randomised, non-inferiority phase 3b trial.	
Participants	472 participants aged ≥ 18 years with symptomatic ST (≥ 5 cm in a supragenual superficial-vein segment) and ≥ 1 additional risk factor for thromboembolic complications (aged ≥ 65 years, male sex, previous VTE, cancer, autoimmune disease, thrombosis of non-varicose veins).	
Interventions	Rivaroxaban (10 mg oral od). Fondaparinux (2.5 mg sc od). Study treatment given for 45 days.	
Outcomes	Primary efficacy outcome: composite of symptomatic DVT or PE, progression or recurrence of ST, and all-cause mortality at 45 days. Secondary efficacy outcomes: composite primary efficacy outcome at 90 days, incidence of each component of the primary efficacy outcome at 45 and 90 days; major VTE (symptomatic PE, symptomatic proximal DVT, or VTE-related death) at days 45 and 90; and surgery for ST within 45 and 90 days of initiation of study drug treatment. Primary safety outcome: major bleeding. Secondary safety outcomes: clinically relevant non-major bleeding, and minor bleeding within 45 days of initiation of treatment with study drug, censored 2 days after the last dose of study drug.	
Notes	Funding: GWT-TUD and Bayer Vital.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate method of randomisation. Quote: "Randomisation was done with a central block randomisation process, with a random block sequence of four numbers per block."

Beyer-Westendorf 2017 (Continued)

Allocation concealment (selection bias)	Low risk	Participants and investigators could not foresee treatment allocation. Quote: "The generation of the allocation sequence to assign all patients to the two treatment groups and the allocation were done at the sponsor's site by the study manager, who had no role in the trial or in data collection or analysis."
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study with blinded outcome assessment. Quote: "An independent committee, whose members were unaware of study group assignment, adjudicated the qualifying diagnosis, the anatomical extent of the initial superficial-vein thrombosis, and all suspected outcomes."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary analysis originally planned as ITT, but modified into a per-protocol analysis during study. 36/471 (7.6%) participants randomised were excluded from the primary analysis but the authors reported results also according to the ITT principle. Quote: "The original study protocol specified that the primary efficacy analysis would be done in the intention-to-treat population; however, the protocol was changed by the steering committee on June 15, 2016, to specify analysis in the per-protocol population."
Selective reporting (reporting bias)	Low risk	All outcome described in the methods and protocol were presented in the results.

Boehler 2014

Methods	Prospective, single-centre, open-label, randomised study.
Participants	73 outpatients with isolated superficial vein thrombosis of the legs. Thrombus length ≥ 5 cm and confirmed by compression ultrasonography. Mean age 56.3 years (SD 13.2) in compression stockings group and 60.3 years (SD 14.8) in control group.
Interventions	Thigh-length compression stockings, class II (23-32 mmHg; Venotrain, Bauerfeind, Zeulenroda, Germany) for 3 weeks. No compression.
Outcomes	Primary outcome: reduction of spontaneous and induced pain as assessed by a VAS and Lowenberg test. Secondary outcomes: consumption of analgesics, thrombus length, skin erythema, D-dimer, and quality of life through the SF-36. Main safety outcomes: symptomatic or asymptomatic DVT and HIT.
Notes	All participants received LMWH at prophylactic dosage (enoxaparin 40 mg/day). NSAIDs (mefenamic acid, diclofenac, and dexibuprofen) were allowed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported. "The randomization procedure was performed in a 1:1 ratio in blocks of 20 with closed envelopes."

Boehler 2014 (Continued)

Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were sealed and sequentially numbered. "The randomization procedure was performed in a 1:1 ratio in blocks of 20 with closed envelopes, with the investigators not being aware of the sequence within the envelopes."
Blinding (performance bias and detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) All outcomes	High risk	7/80 (8.7%) participants initially enrolled were excluded from the analysis due to missing data during follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in methods section were reported in results section of the study publication.

Cosmi 2012

Methods	STEFLEX: multicentre, randomised, double-blind, placebo-controlled study.
Participants	664 consecutive outpatients with ≥ 4 cm long ST of long or short saphenous veins or their collaterals confirmed by CUS. ST of the long saphenous or short saphenous vein within 3 cm to, respectively, the sapheno-femoral or sapheno-popliteal junction were excluded. Median age 69 years (range 20-94 years); males 37% (246/664).
Interventions	Intermediate-dose LMWH (parnaparin 8500 IU od) for 10 days followed by placebo for 20 days. Intermediate-dose LMWH (parnaparin 8500 IU od for 10 days followed by 6400 IU od for 20 days). Prophylactic-dose LMWH (parnaparin 4250 IU od) for 30 days.
Outcomes	Primary efficacy outcomes: composite of symptomatic and asymptomatic DVT, symptomatic PE and relapse, symptomatic or asymptomatic SVT recurrence, or a combination in first 33 days. Secondary efficacy outcomes: reduction in local symptoms during treatment, combined efficacy endpoint during a follow-up of 93 days after the start of treatment. Primary safety outcomes: major bleeding. Secondary safety outcomes: composite of minor bleeding, thrombocytopenia or any other adverse events (e.g. local allergic reactions).
Notes	Participants were instructed to wear graduated elastic stockings (knee high or thigh length) with a compression of 20-40 mmHg at the ankle, unless contraindicated. Oral or topical NSAIDs were permitted for only 4 days after study inclusion. Only paracetamol, naproxen, or ibuprofen were allowed. Study prematurely interrupted according to predefined stopping rules. Funding: study supported by the non-profit organisation Angioclot in the Department of Angiology and Blood Coagulation, S. Orsola Malpighi University Hospital through an unrestricted grant by Alfa Wassermann, Bologna, Italy which had no input into study design; analysis and interpretation of data; writing of the report; and decision to submit the article for publication. Alfa Wassermann provided the study drug and placebo. Disclosure of potential COI: 3 authors including the lead author reported to have received consulting fees from Alfa Wasserman.

Risk of bias

Treatment for superficial thrombophlebitis of the leg (Review)

Cosmi 2012 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation sequence: "The randomization sequence was computer generated centrally in blocks of six."
Allocation concealment (selection bias)	Low risk	Central computer-generated randomisation sequence: "The randomization sequence was computer generated centrally in blocks of six and centers were provided with consecutively numbered boxes of identically appearing prefilled syringes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. "Consecutive outpatients were randomly assigned to receive in a double-blind fashion one of the following subcutaneous treatments." "All primary and secondary outcomes were evaluated by a central adjudication committee, whose members were not involved in patient recruitment."
Incomplete outcome data (attrition bias) All outcomes	High risk	16/664 (2.4%) participants excluded from the analysis, 8 lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

De Sanctis 2001

Methods	Placebo-controlled RCT.
Participants	30 participants with ST confirmed by colour duplex ultrasonography and varicose veins; mean age 51 years; 17 males, 13 females. Not reported if participants were hospitalised or non-hospitalised.
Interventions	Essaven gel (5 cm of gel). Placebo (5 cm of gel). Study treatment given for 4 weeks.
Outcomes	Mean decrease in temperature, mean symptomatic score (local pain, disability, swelling).
Notes	All participants received LMWH (clexane 0.1 mL/10 kg of bodyweight od) for 4 weeks and elastic compression stockings. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "the randomization process was controlled by an external statistical controller according to GCP rules."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias)	Low risk	Double-blind study. "Placebo comparable to Essaven gel was used," "operators were unaware of the contents of the tube."

Treatment for superficial thrombophlebitis of the leg (Review)

De Sanctis 2001 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Decousus 2010b

Methods	CALISTO: multicentre, randomised, double-blind, placebo-controlled study, ITT analysis.
Participants	3002 hospitalised or non-hospitalised participants, aged ≥ 18 years, with acute, symptomatic lower limb superficial-vein thrombosis ≥ 5 cm long, as confirmed by standardised compression ultrasonography. Mean age 57.1 (SD 13.3) years fondaparinux and 56.9 (SD 13.6) years placebo. 1084 males, 1918 females.
Interventions	Fondaparinux (2.5 mg sc od). Placebo. Study treatment given for 45 days.
Outcomes	Primary efficacy outcome: composite of death from any cause or symptomatic PE, symptomatic DVT, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis at day 47. Secondary efficacy outcomes: composite primary efficacy outcome up to day 77 and the following outcomes up to day 47 and 77: each component of the primary efficacy outcome, the composite of symptomatic PE or DVT, and surgery for ST. Primary safety outcome: major bleeding. Secondary safety outcomes: clinically relevant non-major, minor, total (any) bleeding, arterial thromboembolic events, adverse events.
Notes	In the fondaparinux group, 83.0% of participants received graduated compression stockings, 41.5% topical NSAIDs, 3.9% topical anticoagulant drugs, 2.1% oral NSAIDs or COX-2 inhibitors, 1.1% oral or parenteral anticoagulant drugs, 21.4% aspirin or other antiplatelet agents. The corresponding values in the placebo group were similar (83.1%, 41.8%, 3.3%, 3.7%, 6.4%, and 22.6%) except for anticoagulant drugs and oral NSAIDs, which were prescribed more frequently than in the fondaparinux group. Funding: study funded by GlaxoSmithKline, which collected and analysed the data. Disclosure of potential COI: all authors reported to have received grant support and supporting fees from GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based. "computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	Central allocation. "with the use of a central telephone system and a computer-generated randomization list, consecutive participants were randomly assigned..."

Treatment for superficial thrombophlebitis of the leg (Review)

Decousus 2010b (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study. "Fondaparinux and placebo were packaged in identical boxes containing visually identical, prefilled 0.5-ml single-dose syringes." "All symptomatic outcomes were reviewed by the central adjudication committee, whose members were unaware of the patients' group assignments." "The database of adjudicated outcomes was managed by an independent central adjudication committee."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analyses performed on data from the ITT data. Safety analyses performed on data from the as-treated population. Overall, 18 participants in fondaparinux group (1.2%) and 22 in placebo group (1.5%) did not have a primary efficacy assessment. Overall, 1.8% of randomised participants did not complete follow-up. Safety analysis. "1499 patients in the fondaparinux group (99.8%) and 1488 in placebo group (99.2%) were included in the safety analyses."
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Ferrari 1992

Methods	Single centre, open RCT.
Participants	50 participants with acute ST; 22 males, 28 females; median age 52 years. Not reported if participants were hospitalised or non-hospitalised or if the diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Nimesulide (100 mg bid). Diclofenac sodium (50 mg bid). Study treatment given for 10 days.
Outcomes	Spontaneous pain, hyperaemia, oedema, local hyperaemia, fever, tolerability.
Notes	All participants received prophylaxis with heparin calcium. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. "randomly allocated to oral treatment."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote from abstract: "Double-blind study." However, blinding not mentioned in methods, results or discussion sections. Not reported who was blinded and how blinding was attempted.
Incomplete outcome data (attrition bias)	High risk	Overall, 3 participants were not analysed for efficacy outcomes (6%): 2 participants in nimesulide group and 1 in diclofenac group.

Treatment for superficial thrombophlebitis of the leg (Review)

Ferrari 1992 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
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Gorski 2005

Methods	Multicentre, open, RCT; 7- to 14-day follow-up.
Participants	46 non-hospitalised participants with symptomatic ST confirmed by duplex ultrasonography with first symptoms not earlier than 72 hours before inclusion; 15 males, 31 females; mean age 52.5 years.
Interventions	Topical liposomal heparin spray gel (4 puffs of 458 IU tid). LMWH (enoxaparin 40 mg sc od). Study treatment given for 7 or 14 days.
Outcomes	Primary outcomes: DVT, pain scoring, erythema, safety, tolerance. Not specified if DVTs were symptomatic or asymptomatic. Secondary outcomes: participant and investigator assessment of efficacy of treatment.
Notes	Paracetamol up to 1000 mg/day and compression therapy permitted and documented. Funding: study sponsored by CSC Pharmaceuticals Handelsges, Austria. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patient randomization was performed according to a prespecified randomization list."
Allocation concealment (selection bias)	Unclear risk	"Each patient...was allocated to a treatment group according to the next free number on the randomization list." Not reported if allocation done centrally.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study: "treatment were administered in an open way, there was no blinding."
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants lost to follow-up (10%).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Holzgreve 1989

Methods	RCT.
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Treatment for superficial thrombophlebitis of the leg (Review)

Holzgrevé 1989 (Continued)

Participants	60 participants with ST of the legs; 17 males, 43 females; mean age 53.4 years (SD 12). Not reported if participants were hospitalised or non-hospitalised or if diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Etofenak gel. Diclofenac gel.
Outcomes	Length of superficial venous thrombosis, pain, redness, palpable veins, oedema.
Notes	All participants had compression therapy. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blinded. Authors stated it was a single-blind study, and the participants received medication that was labelled as "trial medication." Unclear from paper whether trial physician was blinded to treatment, and since the outcome was symptom improvement, there was a high risk of detection bias by imperfect blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	20 (33%) participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Incandela 2001

Methods	Multicentre, placebo-controlled RCT.
Participants	30 participants with ST confirmed by colour duplex ultrasonography and varices; 14 males, 16 females; mean age 54 years. Not reported if participants were hospitalised or non-hospitalised.
Interventions	Essaven gel (5 cm of gel). Placebo (5 cm of gel). Study treatment given for 8 weeks.
Outcomes	Analogue clinical/symptomatic score including pain, tenderness, disability, local swelling, erythema, presence of thrombosis.
Notes	All participants received LMWH (enoxaparin 0.1 mL/10 kg of bodyweight od) for initial 4 weeks of study and elastic compression stockings for study period.

Incandela 2001 (Continued)

Funding: not reported.

Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear method of random sequence generation: "randomisation process was controlled by an external statistical controller."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. "Placebo comparable to Essaven gel was used," "operators were unaware of the contents of the tube."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all participants included were analysed.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported.

Katzenschlager 2003

Methods	Multicentre, open RCT.
Participants	42 non-hospitalised participants with ST diagnosed by duplex ultrasonography with signs and symptoms lasting < 72 hours; 11 males, 31 females; mean age 52 years.
Interventions	Topical liposomal heparin spray gel (Lipohep 2400 IU/g, 4 spray puffs tid) plus compressive stockings. LMWH (enoxaparin 40 mg sc) plus compressive stockings. Study treatment given for 7-14 days.
Outcomes	Median pain (VAS scale), median area of erythema, thrombus size.
Notes	Participants received paracetamol (1000 mg/day) as pain rescue medication. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The assignment of patients to treatment was done accordingly to a randomisation list using a validated system."
Allocation concealment (selection bias)	Unclear risk	"Each valid subject...was assigned to the next number on the randomization list." Unclear if allocation was done centrally.

Katzenschlager 2003 (Continued)

Blinking (performance bias and detection bias) All outcomes	High risk	Open study: "treatments were administered in a open randomised way."
Incomplete outcome data (attrition bias) All outcomes	High risk	3 (7%) participants, all in the heparin spray gel group, lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Koshkin 2001

Methods	Placebo-controlled, double-blinded RCT.	
Participants	119 participants with acute ST confirmed by duplex ultrasonography; mean age 54.5 years. Not reported if participants were hospitalised or non-hospitalised.	
Interventions	Systemic enzyme therapy (Wobenzym) (10 tablets tid). Placebo. Study treatment given for 16 days.	
Outcomes	Positive changes for a combined outcome including pain, redness, oedema.	
Notes	Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinking (performance bias and detection bias) All outcomes	Unclear risk	Double-blind study; however, not reported who was blinded and how blinding was obtained.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided. Unclear if all included participants were evaluated for study outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Kuhlwein 1985

Methods	Multicentre, placebo-controlled RCT.	
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Treatment for superficial thrombophlebitis of the leg (Review)

Kuhlwein 1985 (Continued)

Participants	76 participants with ST, diagnosed on signs and symptoms only by general practitioners or internists. Not reported if some participants were hospitalised. No data on sex or age reported.
Interventions	Vasotonin forte. Placebo. Study treatment given for 3 weeks.
Outcomes	Overall score including pain, redness, swelling, movement improvement.
Notes	Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind study. Authors stated in abstract that study was double-blind and placebo-controlled. However, no details regarding study medication or placebo given in text.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appeared that after 3 weeks there were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Lozano 2003

Methods	Open RCT.
Participants	60 participants with saphenous proximal thrombophlebitis confirmed by Doppler ultrasonography; 22 males, 38 females; mean age 59 years. Not reported if participants were hospitalised or non-hospitalised.
Interventions	LMWH (enoxaparin 1 mg/kg bid for first week, then 1 mg/kg for 3 weeks) on an outpatient basis. Saphenofemoral disconnection with short hospital stay.
Outcomes	Resolution of symptoms and signs, ST recurrence, VTE, complications from treatment, socioeconomic assessment. Not specified if VTE and ST recurrence were symptomatic or asymptomatic.
Notes	In the immediate postoperative period, compression bandages/elastic stockings used and early walking recommended. Pain was controlled with oral paracetamol 500 mg. Compressive bandage/elastic stockings continued at home by all participants. Funding: not reported.

Lozano 2003 (Continued)

Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 (5%) participants, all in saphenofemoral disconnection group, lost to follow-up.
Selective reporting (reporting bias)	High risk	No information provided on the resolution of signs and symptoms.

Marchiori 2002

Methods	Single-centre RCT.	
Participants	60 consecutive participants with ST of great saphenous vein confirmed by ultrasonography; 26 males, 34 females; mean age 62 years. Not reported if participants were hospitalised or non-hospitalised.	
Interventions	UFH (12,500 IU sc for 1 week then 10,000 IU). UFH (5000 IU). Study treatment given for 4 weeks.	
Outcomes	Asymptomatic and symptomatic recurrence or extension of ST and VTE (or both recurrence and extension) after treatment and at 3 and 6 months. Safety outcomes: major bleeding, HIT, overall mortality.	
Notes	Systemic or local anti-inflammatory drugs (or both) allowed. Funding: not reported. Disclosure of potential COI: the authors report no COI.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based: "List generated by a computer."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.

Marchiori 2002 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Ultrasound assessment performed by blinded investigators. However, not reported if participants and investigators evaluating all other events were blind to study treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Marshall 2001

Methods	Multicentre, placebo-controlled RCT.	
Participants	159 participants with acute ST of leg, diagnosed on symptoms and signs only; 40 males, 116 females; mean age 53.8 years. Not reported if participants were hospitalised or non-hospitalised.	
Interventions	Wobenzym (4 tablets tid). Placebo. Study treatment given for 12-16 days.	
Outcomes	Reduction of pain to day 7 which had to amount to at least 4 points on the VRAS at baseline.	
Notes	LMWH was allowed and administered to 4 participants. Paracetamol (maximal 2 g/day) + compression stockings were given to all participants. 9 participants had already been treated with other medications (no further details), which were stopped before the administration of study treatment. 4 participants had received LMWH before inclusion and continued LMWH throughout study. Funding: not stated. Disclosure of potential COI: not reported, no COI forms available.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based. Participants assigned to treatment with a list generated by a computer.
Allocation concealment (selection bias)	Low risk	Participants assigned to treatment with a list generated by a computer. Concealment of allocation was present since randomisation took place with a computer program called "Random V.5" by Firma Wiedey GmbH Konstanz.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study. Study medication described as "similarly looking study medication [placebo]."
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant withdrew consent postrandomisation; 10 (6%) participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Treatment for superficial thrombophlebitis of the leg (Review)

Messa 1997

Methods	Single-centre, open RCT.
Participants	30 participants with ST; 7 males, 23 females; aged 32-72 years. Not reported if participants were hospitalised or non-hospitalised or if diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Heparansulphate (100 mg tid orally). Sulodexide (250 lipasemic units bid, orally). Study treatment given for 2 weeks.
Outcomes	Redness of the skin, pain, itching, oedema, trophism.
Notes	Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants assigned to treatment with a random list.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study. "The study was performed in a open-label...design."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Nocker 1991

Methods	Placebo-controlled RCT.
Participants	30 participants with unilateral ST of the legs diagnosed on symptoms and signs only; 8 males, 12 females; mean age 59.7 (SD 7.1) years in intervention group; 54.6 (SD 5.6) years in placebo group. Not reported if participants were hospitalised or non-hospitalised.
Interventions	Diclofenac gel (diclofenac 1 g/100 g gel) tid. Placebo tid. Study treatment given for 3 weeks.
Outcomes	Efficacy measured by volume change relative to baseline (difference between the affected and unaffected leg) and reduction in pain described by a VAS; tolerability.

Nocker 1991 (Continued)

Notes Heparin gel given to 10 participants, without randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind study. Authors stated that study was double-blind and placebo-controlled. However, no details regarding study medication or placebo given in main text.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Nusser 1991

Methods	RCT.
Participants	60 participants with ST diagnosed on symptoms and signs only; 25 males, 34 females; mean age 53 (SD 13) years in acemetacin group and 53 (SD 16) years in diclofenac group. Not reported if participants were hospitalised or non-hospitalised.
Interventions	Oral acemetacin (60 mg tid). Oral diclofenac (50 mg tid). Study treatment given until symptoms resolved for maximally 15 days.
Outcomes	Area of ST, pain, redness, palpable venous induration, oedema.
Notes	All participants received compression stockings. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.

Nusser 1991 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study. "similarly looking study medication."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all included participants were evaluated for study outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Pinto 1992

Methods	Multicentre, placebo-controlled RCT.
Participants	68 participants with ST; mean age 42 years. Not reported if participants were hospitalised or non-hospitalised or if the diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Topical 5'-methylthioadenosine 0.5% (0.1 mL/cm skin tid). Placebo. Study treatment given for 1 week.
Outcomes	Oedema, erythema, pain, functional impairment, sc induration, tolerability, VAS score.
Notes	No compression therapy allowed during study. People with ST represent a subgroup of a larger RCT, which included also people with chronic venous insufficiency or second-degree haemorrhoids. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study. "indistinguishable placebo."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all included participants were evaluated for study outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Rathbun 2012

Methods	Randomised, controlled, double-blind, double-dummy trial.
Participants	72 consecutive inpatient and outpatients with ST of the lower (57 participants) or upper extremities confirmed by ultrasonography in the absence of a current intravenous catheter. ST involved lower extremities in 27/37 participants in dalteparin group and in 30/35 in ibuprofen group. Mean age 51 years (range 28-88) in dalteparin group and 52 years (range 19-85) in ibuprofen group. 21 males, 51 females.
Interventions	<p>LMWH (dalteparin 200 IU/kg at presentation followed by a fixed dose of 10,000 units sc daily for additional 6-13 days) + placebo given orally tid for 7 days.</p> <p>Ibuprofen 800 mg orally tid for up to 14 days + placebo injection od for 7 days.</p> <p>If symptoms of ST were not resolved at day 7-9, in the absence of thrombus extension, participant received an additional 7 days of blind therapy. If symptoms of ST were resolved at day 7-9 in the absence of thrombus extension, study medication was stopped.</p> <p>If at any time thrombus extended either superficially or into deep venous system, study treatment was discontinued and full therapeutic anticoagulation with iv heparin or LMWH started.</p>
Outcomes	<p>Primary efficacy outcomes: incidence of thrombus extension or new symptomatic VTE during 14-day and 3-month follow-up period.</p> <p>Secondary efficacy outcomes: reduction in pain, evaluated through the 11-point Box Pain scale, from baseline to day 7 and 14- to 16-day follow-up.</p> <p>Safety outcomes: incidence of major and minor bleeding.</p>
Notes	<p>Compression stockings not routinely prescribed.</p> <p>Funding: grant from the National Center for Research Resources, National Institute of Health and Pfizer Inc for provision of dalteparin, ibuprofen, and nurse personnel salary support.</p> <p>Disclosure of potential COI: the authors reported no COI.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Balanced randomization blocks of four each consisting of equal numbers" for the 2 treatment groups.
Allocation concealment (selection bias)	Low risk	"Randomization...was performed by the investigational pharmacist within 24 h of presenting with a confirmed diagnosis..."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. "The patient, research assistant and principal investigator were blinded to the treatment group."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all included participants were evaluated for study outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Spirkoska 2015

Methods	Randomised, double-blind, controlled, single-centre trial. Recanalisation of veins in superficial vein thrombosis (REVETR) study.
Participants	68 participants with ultrasonographically confirmed first symptomatic acute SVT of the lower extremities without concomitant DVT or PE. Mean age 60.2 (SD 11.2) years; males: 31 (46%).
Interventions	LMWH (dalteparin 5000 IU) sc od. LMWH (dalteparin 10,000 IU) sc od. Both groups received treatment with study drug for 6 weeks. Quote: "All patients were advised to remain active and to use ECBs or elastic compression stockings up to the thigh (30-40 mm Hg of compression) for the whole study period."
Outcomes	Primary: change in the diameter and length of thrombus. Secondary: recurrent ST, DVT, PE, major bleeding.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were individually randomized by a computer generated random allocation sequence." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were individually randomized by a computer generated random allocation sequence." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "All participants and investigators were masked to treatment assignment and also blind to the size of each block." Comment: reported as a double-blind study; however, not stated that the 2 dosages of study drug had identical appearance.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In all, 3 (5%) patients were excluded from further follow-up after the diagnosis of active cancer." Comment: at least 5% of participants randomised were subsequently excluded from the analysis.
Selective reporting (reporting bias)	High risk	Comment: authors reported that ST recurrence was a secondary outcome; however, no information about occurrence of this outcome given in results section of study publication.

Stenox Group 2003

Methods	STENOX: multicentre, placebo-controlled RCT with 3-month follow-up, ITT analysis.
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Stenox Group 2003 (Continued)

Participants	427 hospitalised or non-hospitalised participants with ST of ≥ 5 cm on ultrasonography examination; 156 males, 271 females; mean age 62 years.
Interventions	LMWH (enoxaparin 40 mg sc od). LMWH (enoxaparin 1.5 mg/kg sc od). Oral tenoxicam (20 mg od). Placebo. Study treatment given for 8-12 days.
Outcomes	Primary efficacy outcome: symptomatic PE and symptomatic and asymptomatic DVT at 12 days. Secondary efficacy outcomes: symptomatic and asymptomatic recurrence or extension of ST (or both) at 12 days and 3 months; symptomatic PE and symptomatic and asymptomatic DVT at 12 days and 3 months (97 days). Safety outcomes: death, major and minor bleeding, thrombocytopenia, and any other adverse event.
Notes	All participants used elastic bandages or support stockings from day 1 of therapy and continued for at least 15 days. Participants requiring anticoagulant therapy, ligation of the saphenofemoral junction or thrombectomy, anticoagulants or NSAIDs for > 48 hours excluded from study. Study prematurely interrupted due to slow recruitment rate. Funding: Laboratoires Aventis, Paris and Association Française de Formation Continue en Angiologie, Paris. Disclosure of potential COI: authors reported no financial interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear method of sequence generation: "patients were centrally randomly assigned to receive..."
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study: "study medications were packaged in boxes of identical appearance." "all boxes had visually identical contents." "outcomes were reviewed blindly by an independent critical event committee."
Incomplete outcome data (attrition bias) All outcomes	High risk	9/436 (2%) participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Titon 1994

Methods	Multicentre, open RCT.
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Titon 1994 (Continued)

Participants	117 non-hospitalised participants with ST confirmed by ultrasonography; 25 males, 92 females; age range 54-64 years. Mean ages varied between groups, particularly for the few men in the dose-adjusted group of nadroparin who were much younger than the men in the other 2 groups.
Interventions	Naproxen (oral 500 mg od). LMWH (nadroparin 0.6 mL/6150 anti-Xa IU od). LMWH (nadroparin 61.5 anti-Xa IU/kg sc od). Study treatment given for 6 days.
Outcomes	Primary efficacy: recurrence or extension (or both) of ST, VTE after treatment (day 7) and after 8 weeks. Secondary efficacy outcomes: symptoms (pain and functional disability) and signs (erythema, oedema). Safety outcomes: major and minor bleeding.
Notes	All participants received elastic stockings for the first 7 days. Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study. "open trial."
Incomplete outcome data (attrition bias) All outcomes	High risk	At day 7, 0 participants were lost to follow-up. 4 (3.4%) participants were not evaluated by ultrasonography. At 8 weeks, 8 (6.8%) participants were lost to follow-up and 25 (21%) participants were not evaluated by ultrasonography.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Uncu 2009

Methods	Open RCT
Participants	50 participants with ST of greater saphenous vein of ≥ 5 cm in length on duplex ultrasonography. Not reported if participants were hospitalised or non-hospitalised. Mean age: 48.6 (range 25-90) years in Ca-nadroparin and 44.9 (28-85) years in Ca-nadroparin + acemetacin. 27 males, 23 females.
Interventions	LMWH (Ca-nadroparin 190 IU Axa/kg od). LMWH (Ca-nadroparin 190 IU Axa/kg od) + acemetacin (60 mg oral bid).

Uncu 2009 (Continued)

Study treatment given for 10 days.

Outcomes	Primary outcomes: spontaneous pain, erythema, local tenderness, palpable cord.
Notes	Funding: not reported. Disclosure of potential COI: not reported, no COI forms available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternation: "consecutive alternating method."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No information provided about blinding, but likely an open study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors did not report if they performed an ITT analysis and unclear whether study outcomes were evaluated in all included participants.
Selective reporting (reporting bias)	High risk	All prespecified outcomes reported. Symptomatic DVT, PE, ST extension, bleeding, death, and adverse events reported in results but not mentioned in methods section.

Vesalio Group 2005

Methods	VESALIO: multicentre, double-blind, double-dummy RCT, ITT analysis.
Participants	164 hospitalised or non-hospitalised participants with ST of great saphenous vein with the thrombosis extending up to 3 cm from the saphenous-femoral junction; 60 males, 104 females; mean age 63 years. Diagnosis of ST objectively confirmed by compression ultrasonography.
Interventions	Weight-adjusted LMWH (nadroparin full dose for 10 days followed by half dose for 20 additional days). Fixed-dose LMWH (nadroparin 2850 anti-Xa IU). Study treatment given for 30 days.
Outcomes	Primary efficacy outcome: asymptomatic and symptomatic extension of ST or VTE (or both) in a 3-month follow-up period. Secondary efficacy outcomes: clinical signs and symptoms. Primary safety outcomes: major bleeding, HIT.
Notes	No aspirin or NSAIDs use throughout study. Study prematurely interrupted due to slow recruitment rate. Funding: grant from Sanofi-Synthelabo, Sanofi Aventis Group, Milano and GlaxoSmithKline, Verona. Disclosure of potential COI: the authors declared no COI.

Vesalio Group 2005 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based: "each patient was assigned a unique sequential subject number, generated by a computer."
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes, not clear if opaque. "Each center received a initial fixed amount of randomization numbers and corresponding sealed envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study. "Placebo identical in appearance to nadroparin." "all suspected outcome events were reviewed and classified by a Central Adjudication Committee whose members were unaware of treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.

Winter 1986

Methods	Multicentre, randomised trial.
Participants	100 people with ST. Not reported if participants were hospitalised or non-hospitalised or if the diagnosis of ST was objectively confirmed by ultrasonography.
Interventions	Diclofenac emulgel. Heparin gel. Study treatment given 14 days.
Outcomes	Pain (spontaneous and after pressure), redness, palpable cord.
Notes	Study only reported as an abstract for a scientific meeting. No full paper available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information on study medication or outcome assessment provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors did not report whether they performed an ITT analysis.

Winter 1986 (Continued)

Selective reporting (re-reporting bias) Unclear risk Outcomes not specified, only a general outcome of "efficacy" reported.

bid: twice daily; COI: conflicts of interest; COX: cyclo-oxygenase; CUS: compression ultrasound; DVT: deep vein thrombosis; ECB: elastic compression bandage; HIT: heparin-induced thrombocytopenia; im: intramuscularly; ITT: intention to treat; IU: international units; LMWH: low molecular weight heparin; NSAID: non-steroidal anti-inflammatory drug; od: once daily; PE: pulmonary embolism; RCT: randomised controlled trial; sc: subcutaneously; SD: standard deviation; SF-36: 36-item Short Form; ST: superficial thrombophlebitis; tid: three times daily; UFH: unfractionated heparin; VAS: visual analogue scale; VRAS: visual rating analogue scale; VRS: visual rating scale.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agus 1993	Impossible to extract outcomes data separately for the 2 study treatment groups.
Alleggra 1981	Mixed population. Impossible to extract data separately for the ST.
Annoni 1991	Mixed population. Impossible to extract data separately for ST.
Argentero 1983	Mixed population including people with DVT. Impossible to extract data separately for ST.
Bagliani 1983	Mixed population including also people with DVT. Impossible to extract data separately for ST.
Becherucci 2000	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for ST of the lower limbs.
Bergqvist 1990	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for ST of the lower limbs.
Bernicot 1980	People without a diagnosis of ST of the legs.
Bijuan 2003	Likely people with acute ST of the upper limb. However, impossible to judge eligibility fully due to unavailability of the full text.
Bracale 1996	Mixed population including also people with DVT. Impossible to extract data separately for the ST.
Bruni 1979	Mixed population including also people with acute ST of the upper limb. Impossible to extract data separately for the ST of the lower limbs.
Della Marchina 1989	Mixed population including also people with DVT and post-phlebotic syndrome. Impossible to extract data separately for the ST.
Di Perri 1986	People with DVT.
Gandhi 1984	People without a diagnosis of ST of the legs.
Giorgetti 1990	Single-blind study of people with varicophlebitis who received either Seaprose S or placebo. Unclear whether study was randomised or not.
Gouping 2003	People with postinfusion ST of the arm.
Ibanez-Bermudez 1996	Evaluated outcomes not among those evaluated in present review.
Luttichau 1989	Mixed population. Impossible to extract data separately for ST.

Study	Reason for exclusion
Mari 1982	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for ST of the lower limbs.
Marsala 1985	Mixed population. Impossible to extract data separately for ST.
Mauro 1992	Mixed population including people with DVT. Impossible to extract data separately for ST.
Mehta 1975	People with ST of the arm.
Ng 2010	People with ST of the arm.
Paciaroni 1982	Mixed population including people with chronic venous insufficiency. Impossible to extract data separately for ST.
Porters 1981	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for ST of the lower limbs.
Pozza 1980	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for ST of the lower limbs.
Rea 1981	People with DVT.
Resta 1967	People without a diagnosis of ST of the legs.
Rozsos 1994	People with ST of the arm.
Seccia 1989	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for the ST of the lower limbs.
Seghezzi 1972	Mixed population including people with DVT and recurrent postphlebotic syndromes. Impossible to extract data separately for ST of the lower limbs.
Seligman 1969	Mixed population including people with DVT. Impossible to extract data separately for ST.
Stolle 1986	Mixed population including people with acute ST of the upper limb. Impossible to extract data separately for the ST of the lower limbs.
Supe 2013	People with ST of the arm.
Tomamichel 1983	Mixed population including people with DVT. Impossible to extract data separately for ST.
van Cauwenberge 1972	People without a diagnosis of ST of the legs.
van der Knaap 1988	People with ST of the arm.

DVT: deep vein thrombosis; ST: superficial thrombophlebitis.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Cazaubon 2013](#)

Methods	Not available.
Participants	Not available.

Cazaubon 2013 *(Continued)*

Interventions	Not available.
Outcomes	Not available.
Notes	Unable to retrieve the abstract or the full text.

Wac 2001

Methods	Not available.
Participants	Not available.
Interventions	Not available.
Outcomes	Not available.
Notes	Unable to retrieve the abstract or the full text.

Xu 2001

Methods	Not available.
Participants	Not available.
Interventions	Not available.
Outcomes	Not available.
Notes	Unable to retrieve the abstract or the full text.

Characteristics of ongoing studies *[ordered by study ID]*
Rabe 2009

Trial name or title	DAPS-Dalteparin in Patients with Superficial Leg Vein Phlebitis in Addition to Compression Treatment - a Placebo-Controlled Phase III Study.
Methods	Randomised, double-blind, multicentre, phase III trial.
Participants	276 participants with superficial leg vein phlebitis.
Interventions	Compression stockings (30 mmHg) for 3 months and either dalteparin 10,000 IU (group A) or placebo (group B) for 14 days.
Outcomes	Primary endpoint: progression of the thrombotic process during treatment period as confirmed by ultrasound. Sonographic assessment planned in all participants on days 1, 7, 14, and 90. Secondary endpoints: pain assessment by visual analogue scale and calculation of symptom scores (tension, heaviness, swelling).
Starting date	Not reported.

Treatment for superficial thrombophlebitis of the leg (Review)

Rabe 2009 (Continued)

Contact information

Rabe E.

Notes

DATA AND ANALYSES
Comparison 1. Fondaparinux versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Deep vein thrombosis or pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Extension of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Recurrence of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Clinically relevant non-major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Minor bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Arterial thromboembolic complication	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Adverse effects of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12 Non-fatal serious adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Fondaparinux versus placebo, Outcome 1 Pulmonary embolism.

Analysis 1.2. Comparison 1 Fondaparinux versus placebo, Outcome 2 Deep vein thrombosis.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	3/1502	18/1500		0.17[0.05,0.56]
			Favours fondaparinux	Favours placebo

Analysis 1.3. Comparison 1 Fondaparinux versus placebo, Outcome 3 Deep vein thrombosis or pulmonary embolism.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	3/1502	20/1500		0.15[0.04,0.5]
			Favours fondaparinux	Favours placebo

Analysis 1.4. Comparison 1 Fondaparinux versus placebo, Outcome 4 Extension of superficial thrombophlebitis.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	4/1502	51/1500		0.08[0.03,0.22]
			Favours fondaparinux	Favours placebo

Analysis 1.5. Comparison 1 Fondaparinux versus placebo, Outcome 5 Recurrence of superficial thrombophlebitis.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	5/1502	24/1500		0.21[0.08,0.54]
			Favours fondaparinux	Favours placebo

Analysis 1.6. Comparison 1 Fondaparinux versus placebo, Outcome 6 Mortality.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	2/1502	1/1500		2[0.18,22]
			Favours fondaparinux	Favours placebo

Analysis 1.7. Comparison 1 Fondaparinux versus placebo, Outcome 7 Major bleeding.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	1/1499	1/1488		0.99[0.06,15.86]
			Favours fondaparinux	Favours placebo

Analysis 1.8. Comparison 1 Fondaparinux versus placebo, Outcome 8 Clinically relevant non-major bleeding.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	5/1499	8/1488		0.62[0.2,1.89]
			Favours fondaparinux	Favours placebo

Analysis 1.9. Comparison 1 Fondaparinux versus placebo, Outcome 9 Minor bleeding.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	9/1499	6/1488		1.49[0.53,4.17]
			Favours fondaparinux	Favours placebo

Analysis 1.10. Comparison 1 Fondaparinux versus placebo, Outcome 10 Arterial thromboembolic complication.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	0/1502	3/1500		0.14[0.01,2.76]
			Favours fondaparinux	Favours placebo

Analysis 1.11. Comparison 1 Fondaparinux versus placebo, Outcome 11 Adverse effects of treatment.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	56/1499	49/1488		1.13[0.78,1.65]
			Favours fondaparinux	Favours placebo

Analysis 1.12. Comparison 1 Fondaparinux versus placebo, Outcome 12 Non-fatal serious adverse event.

Study or subgroup	Fondaparinux n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Decousus 2010b	10/1499	16/1488		0.62[0.28,1.36]
			Favours fondaparinux	Favours placebo

Comparison 2. Fondaparinux versus rivaroxaban

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Deep vein thrombosis or pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Extension of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Recurrence of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Clinically relevant non-major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Minor bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Adverse effects of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 1 Pulmonary embolism.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	0/236	0/236		Not estimable
			Favours fondaparinux	Favours rivaroxaban

Analysis 2.2. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 2 Deep vein thrombosis.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	1/236	3/236		0.33[0.03,3.18]
			Favours fondaparinux	Favours rivaroxaban

Analysis 2.3. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 3 Deep vein thrombosis or pulmonary embolism.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	1/236	3/236		0.33[0.03,3.18]
Favours fondaparinux 0.01 0.1 1 10 100 Favours rivaroxaban				

Analysis 2.4. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 4 Extension of superficial thrombophlebitis.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	0/236	0/236		Not estimable
Favours fondaparinux 0.01 0.1 1 10 100 Favours rivaroxaban				

Analysis 2.5. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 5 Recurrence of superficial thrombophlebitis.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	3/236	4/236		0.75[0.17,3.31]
Favours fondaparinux 0.01 0.1 1 10 100 Favours rivaroxaban				

Analysis 2.6. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 6 Mortality.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	0/236	1/236		0.33[0.01,8.14]
Favours fondaparinux 0.01 0.1 1 10 100 Favours rivaroxaban				

Analysis 2.7. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 7 Major bleeding.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	0/235	0/236		Not estimable
Favours fondaparinux 0.01 0.1 1 10 100 Favours rivaroxaban				

Analysis 2.8. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 8 Clinically relevant non-major bleeding.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	1/235	6/236		0.17[0.02,1.38]
Favours fondaparinux				Favours rivaroxaban

Analysis 2.9. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 9 Minor bleeding.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	15/235	15/236		1[0.5,2.01]
Favours fondaparinux				Favours rivaroxaban

Analysis 2.10. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 10 Serious adverse events.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	6/236	13/236		0.46[0.18,1.19]
Favours fondaparinux				Favours rivaroxaban

Analysis 2.11. Comparison 2 Fondaparinux versus rivaroxaban, Outcome 11 Adverse effects of treatment.

Study or subgroup	Fondaparinux n/N	Rivaroxaban n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Beyer-Westendorf 2017	0/235	3/236		0.14[0.01,2.76]
Favours fondaparinux				Favours rivaroxaban

Comparison 3. Prophylactic low molecular weight heparin (LMWH) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 1 Venous thromboembolism end-of-treatment.

Study or subgroup	Prophylactic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	1/110	4/112		0.25[0.03,2.24]
Favours prophylactic LMWH Favours placebo				

Analysis 3.2. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 2 Venous thromboembolism 3-month follow-up.

Study or subgroup	Prophylactic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	6/110	5/112		1.22[0.38,3.89]
Favours prophylactic LMWH Favours placebo				

Analysis 3.3. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	Prophylactic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	16/110	37/112		0.44[0.26,0.74]
Favours prophylactic LMWH Favours placebo				

Analysis 3.4. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 4 Major bleeding.

Study or subgroup	Prophylactic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/110	0/112		Not estimable
Favours prophylactic LMWH Favours placebo				

Analysis 3.5. Comparison 3 Prophylactic low molecular weight heparin (LMWH) versus placebo, Outcome 5 Heparin-induced thrombocytopenia.

Study or subgroup	Prophylactic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/110	0/112		Not estimable
Favours prophylactic LMWH 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Comparison 4. Therapeutic low molecular weight heparin (LMWH) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 1 Venous thromboembolism end-of-treatment.

Study or subgroup	Therapeutic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	1/106	4/112		0.26[0.03,2.33]
Favours therapeutic LMWH 0.01 0.1 1 10 100 Favours placebo				

Analysis 4.2. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 2 Venous thromboembolism 3-month follow-up.

Study or subgroup	Therapeutic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	4/106	5/112		0.85[0.23,3.06]
Favours therapeutic LMWH 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Analysis 4.3. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	Therapeutic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	16/106	37/112		0.46[0.27,0.77]
Favours therapeutic LMWH 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Analysis 4.4. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 4 Major bleeding.

Study or subgroup	Therapeutic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/106	0/112		Not estimable
Favours therapeutic LMWH 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Analysis 4.5. Comparison 4 Therapeutic low molecular weight heparin (LMWH) versus placebo, Outcome 5 Heparin-induced thrombocytopenia.

Study or subgroup	Therapeutic LMWH n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/106	0/112		Not estimable
Favours therapeutic LMWH 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Comparison 5. Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic deep vein thrombosis end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Symptomatic deep vein thrombosis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Extension of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Recurrence of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.

Study or subgroup	30-day intermediate LMWH n/N	30-day prophylactic LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	1/219	3/217		0.33[0.03,3.15]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 30-day prophyl

Analysis 5.2. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.

Study or subgroup	30-day intermediate LMWH n/N	30-day prophylactic LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	4/219	7/217		0.57[0.17,1.91]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 30-day prophyl

Analysis 5.3. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.

Study or subgroup	30-day intermediate LMWH n/N	30-day prophylactic LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	1/219	3/217		0.33[0.03,3.15]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 30-day prophyl

Analysis 5.4. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.

Study or subgroup	30-day intermediate LMWH n/N	30-day prophylactic LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	4/219	6/217		0.66[0.19,2.31]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 30-day prophylac

Analysis 5.5. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.

Study or subgroup	30-day intermediate LMWH n/N	30-day prophylactic LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	5/219	18/217		0.28[0.1,0.73]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 30-day prophyl

Analysis 5.6. Comparison 5 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 30-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.

Comparison 6. Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic deep vein thrombosis end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Symptomatic deep vein thrombosis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Extension of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Recurrence of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.

Analysis 6.2. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.

Analysis 6.3. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.

Study or subgroup	30-day prophylactic LMWH	10-day intermediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	3/217	9/212		0.33[0.09,1.19]
Favours 30-day prophyl Favours 10-day intermed				

Analysis 6.4. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.

Study or subgroup	30-day prophylactic LMWH	10-day intermediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	6/217	10/212		0.59[0.22,1.58]
Favours 30-day prophyl Favours 10-day intermed				

Analysis 6.5. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.

Study or subgroup	30-day prophylactic LMWH	10-day intermediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	18/217	22/212		0.8[0.44,1.45]
Favours 30-day prophyl Favours 10-day intermed				

Analysis 6.6. Comparison 6 Thirty-day prophylactic low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.

Study or subgroup	30-day prophylactic LMWH	10-day intermediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	6/217	15/212		0.39[0.15,0.99]
Favours 30-day prophyl Favours 10-day intermed				

Comparison 7. Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Symptomatic deep vein thrombosis end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Symptomatic deep vein thrombosis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Extension of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Recurrence of superficial thrombophlebitis 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 1 Venous thromboembolism end-of-treatment.

Study or subgroup	30-day intermediate LMWH n/N	10-day intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	1/219	10/212		0.1[0.01,0.75]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 10-day intermed

Analysis 7.2. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 2 Venous thromboembolism 3-month follow-up.

Study or subgroup	30-day intermediate LMWH n/N	10-day intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	4/219	11/212		0.35[0.11,1.09]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 10-day intermed

Analysis 7.3. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 3 Symptomatic deep vein thrombosis end-of-treatment.

Study or subgroup	30-day intermediate LMWH n/N	10-day intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cosmi 2012	1/219	9/212		0.11[0.01,0.84]
Favours 30-day intermed			0.01 0.1 1 10 100	Favours 10-day intermed

Analysis 7.4. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 4 Symptomatic deep vein thrombosis 3-month follow-up.

Study or subgroup	30-day inter- mediate LMWH	10-day inter- mediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	4/219	10/212		0.39[0.12,1.22]

Analysis 7.5. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 5 Extension of superficial thrombophlebitis 3-month follow-up.

Study or subgroup	30-day inter- mediate LMWH	10-day inter- mediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	5/219	22/212		0.22[0.08,0.57]

Analysis 7.6. Comparison 7 Thirty-day intermediate low molecular weight heparin (LMWH) versus 10-day intermediate LMWH, Outcome 6 Recurrence of superficial thrombophlebitis 3-month follow-up.

Study or subgroup	30-day inter- mediate LMWH	10-day inter- mediate LMWH	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cosmi 2012	10/219	15/212		0.65[0.3,1.4]

Comparison 8. Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Symptomatic pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Superficial thrombophlebitis progression into deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 1 Symptomatic venous thromboembolism.

Study or subgroup	Prophylactic LMWH n/N	Intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Spirkoska 2015	0/33	1/35		0.35[0.01,8.37]
Favours prophylactic 0.001 0.1 1 10 1000 Favours intermediate				

Analysis 8.2. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 2 Symptomatic pulmonary embolism.

Study or subgroup	Prophylactic LMWH n/N	Intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Spirkoska 2015	0/33	1/35		0.35[0.01,8.37]
Favours prophylactic 0.001 0.1 1 10 1000 Favours intermediate				

Analysis 8.3. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 3 Superficial thrombophlebitis progression into deep vein thrombosis.

Study or subgroup	Prophylactic LMWH n/N	Intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Spirkoska 2015	1/33	1/35		1.06[0.07,16.27]
Favours prophylactic 0.002 0.1 1 10 500 Favours intermediate				

Analysis 8.4. Comparison 8 Six-week prophylactic low molecular weight heparin (LMWH) versus six-week intermediate LMWH, Outcome 4 Major bleeding.

Study or subgroup	Prophylactic LMWH n/N	Intermediate LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Spirkoska 2015	0/33	0/35		Not estimable
Favours prophylactic 0.01 0.1 1 10 100 Favours intermediate				

Comparison 9. Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Superficial thrombophlebitis or venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism	2	238	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.72]
3 Superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Swelling disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Tenderness disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Pain disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Pitting oedema disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Collateral veins disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Redness disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Palpable cord disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Major bleeding	2	238	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Heparin-induced thrombocytopenia	2	238	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 16.11]

Analysis 9.1. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 1 Superficial thrombophlebitis or venous thromboembolism.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	7/81	6/83		1.2[0.42,3.4]

Analysis 9.2. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 2 Venous thromboembolism.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/38	0/36			Not estimable
Vesalio Group 2005	2/81	4/83		100%	0.51[0.1,2.72]
Total (95% CI)	119	119		100%	0.51[0.1,2.72]
Total events: 2 (Fixed-dose LMWH), 4 (Weight-adjusted LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					

Analysis 9.3. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 3 Superficial thrombophlebitis.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	5/81	2/83		2.56[0.51,12.83]
Favours fixed-dose				Favours weight-adjusted

Analysis 9.4. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 4 Swelling disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	16/19	12/17		1.19[0.83,1.72]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.5. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 5 Tenderness disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	7/10	13/19		1.02[0.62,1.7]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.6. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 6 Pain disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	52/60	59/62		0.91[0.81,1.02]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.7. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 7 Pitting oedema disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	7/9	16/17		0.83[0.57,1.2]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.8. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 8 Collateral veins disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	7/13	9/16		0.96[0.49,1.86]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.9. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 9 Redness disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	59/76	60/76		0.98[0.83,1.16]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.10. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 10 Palpable cord disappearance.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Vesalio Group 2005	26/73	37/74		0.71[0.49,1.05]
Favours weight-adjusted				Favours fixed-dose

Analysis 9.11. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 11 Major bleeding.

Study or subgroup	Fixed-dose LMWH n/N	Weight-adjusted LMWH n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/38	0/36			Not estimable
Vesalio Group 2005	0/81	0/83			Not estimable
Total (95% CI)	119	119			Not estimable
Total events: 0 (Fixed-dose LMWH), 0 (Weight-adjusted LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Favours fixed-dose					Favours weight-adjusted

Analysis 9.12. Comparison 9 Fixed-dose low molecular weight heparin (LMWH) versus weight-adjusted LMWH, Outcome 12 Heparin-induced thrombocytopenia.

Comparison 10. Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 1 Venous thromboembolism.

Analysis 10.2. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Analysis 10.3. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 3 Major bleeding.

Study or subgroup	Therapeutic LMWH n/N	Surgery n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lozano 2003	0/30	0/30		Not estimable

Analysis 10.4. Comparison 10 Therapeutic low molecular weight heparin (LMWH) versus saphenofemoral disconnection, Outcome 4 Complications.

Study or subgroup	Therapeutic LMWH n/N	Surgery n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Lozano 2003	2/30	2/30		1[0.15,6.64]

Comparison 11. Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	2	278	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.24, 3.63]
2 Extension or recurrence (or both) of superficial thrombophlebitis	3	331	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.58, 1.78]
3 Major bleeding	3	335	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Heparin-induced thrombocytopenia	2	278	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism.

Study or subgroup	Fixed-dose LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	4/106	4/99		100%	0.93[0.24,3.63]
Titon 1994	0/38	0/35			Not estimable
Total (95% CI)	144	134		100%	0.93[0.24,3.63]
Total events: 4 (Fixed-dose LMWH), 4 (NSAIDs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)

Analysis 11.2. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Analysis 11.3. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Major bleeding.

Analysis 11.4. Comparison 11 Fixed-dose low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Heparin-induced thrombocytopenia.

Comparison 12. Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism.

Study or subgroup	LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/36	0/35		Not estimable
Favours LMWH 0.1 0.2 0.5 1 2 5 10 Favours NSAIDs				

Analysis 12.2. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/35	0/33		Not estimable
Favours NSAIDs 0.1 0.2 0.5 1 2 5 10 Favours adjust LMWH				

Analysis 12.3. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Major bleeding.

Study or subgroup	LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/36	0/35		Not estimable
Favours LMWH 0.1 0.2 0.5 1 2 5 10 Favours NSAIDs				

Analysis 12.4. Comparison 12 Weight-adjusted low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Heparin-induced thrombocytopenia.

Study or subgroup	LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Titon 1994	0/36	0/35		Not estimable
Favours LMWH 0.1 0.2 0.5 1 2 5 10 Favours NSAIDs				

Comparison 13. Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism end-of-treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Venous thromboembolism 3-month follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 1 Venous thromboembolism end-of-treatment.

Study or subgroup	Prophylactic LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	1/110	2/99		0.45[0.04,4.89]
Favours prophylactic LMWH 0.01 0.1 1 10 100 Favours NSAIDs				

Analysis 13.2. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 2 Venous thromboembolism 3-month follow-up.

Study or subgroup	Prophylactic LMWH n/N	NSAIDs n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	6/110	4/99		1.35[0.39,4.64]
Favours prophylactic LMWH 0.1 0.2 0.5 1 2 5 10 Favours NSAIDs				

Analysis 13.3. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 3 Extension or recurrence (or both) of superficial thrombophlebitis.

Analysis 13.4. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 4 Major bleeding.

Analysis 13.5. Comparison 13 Prophylactic low molecular weight heparin (LMWH) versus non-steroidal anti-inflammatory drugs (NSAIDs), Outcome 5 Heparin-induced thrombocytopenia.

Comparison 14. Low molecular weight heparin (LMWH) versus LMWH plus acemetacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary embolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Extension of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Pain reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Hyperaemia reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Tenderness reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Palpable cord reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Minor bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 14.1. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acetaminophen, Outcome 1 Pulmonary embolism.

Study or subgroup	LMWH n/N	LMWH + acetaminophen n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
			Favours LMWH 0.01 0.1 1 10 100	Favours LMWH +acetaminophen

Analysis 14.2. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acetaminophen, Outcome 2 Deep vein thrombosis.

Study or subgroup	LMWH n/N	LMWH +acetaminophen n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
			Favours LMWH 0.01 0.1 1 10 100	Favours LMWH +acetaminophen

Analysis 14.3. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acetaminophen, Outcome 3 Extension of superficial thrombophlebitis.

Study or subgroup	LMWH n/N	LMWH + acetaminophen n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
			Favours LMWH 0.01 0.1 1 10 100	Favours LMWH +acetaminophen

Analysis 14.4. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acetaminophen, Outcome 4 Pain reduction.

Study or subgroup	LMWH N	LMWH + acetaminophen N	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Uncu 2009	25 5.9 (1.2)	25 5 (1.4)		0.9[0.18,1.62]
			Favours LMWH+acetaminophen -4 -2 0 2 4	Favours LMWH

Analysis 14.5. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 5 Hyperaemia reduction.

Study or subgroup	LMWH		LMWH + acemetacin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Uncu 2009	25	4.4 (1.9)	25	4 (1.7)		0.4[-0.6,1.4]
					Favours LMWH+acemetacin	Favours LMWH

Analysis 14.6. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 6 Tenderness reduction.

Study or subgroup	LMWH		LMWH + acemetacin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Uncu 2009	25	5.3 (2.2)	25	4.2 (1.8)		1.1[-0.01,2.21]
					Favours LMWH+acemetacin	Favours LMWH

Analysis 14.7. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 7 Palpable cord reduction.

Study or subgroup	LMWH		LMWH + acemetacin		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Uncu 2009	25	3.3 (3.4)	25	2.2 (1.5)		1.1[-0.36,2.56]
					Favours LMWH+acemetacin	Favours LMWH

Analysis 14.8. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 8 Mortality.

Study or subgroup	LMWH	LMWH + acemetacin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
			Favours LMWH	Favours LMWH +acemetacin

Analysis 14.9. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 9 Major bleeding.

Study or subgroup	LMWH	LMWH + acemetacin	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
			Favours LMWH	Favours LMWH +acemetacin

Analysis 14.10. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 10 Minor bleeding.

Study or subgroup	LMWH n/N	LMWH + acemetacin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Uncu 2009	0/25	1/25		0.33[0.01,7.81]
Favours LMWH				Favours LMWH +acemetacin

Analysis 14.11. Comparison 14 Low molecular weight heparin (LMWH) versus LMWH plus acemetacin, Outcome 11 Adverse events.

Study or subgroup	LMWH n/N	LMWH + acemetacin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Uncu 2009	0/25	0/25		Not estimable
Favours LMWH				Favours LMWH +acemetacin

Comparison 15. Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus ECS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.

Study or subgroup	ECS + LMWH n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	0/76	6/78		0.08[0.01,1.38]
Favours ECS+LMWH				Favours ECS

Analysis 15.2. Comparison 15 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	ECS + LMWH n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	1/76	13/78		0.08[0.01,0.59]
Favours ECS+LMWH				Favours ECS

Comparison 16. Low molecular weight heparin (LMWH) versus heparin spray gel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.03, 2.70]
2 Participants with thrombus at 21 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Allergic reaction or elevated sedimentation rate	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 1 Deep vein thrombosis.

Analysis 16.2. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 2 Participants with thrombus at 21 days.

Analysis 16.3. Comparison 16 Low molecular weight heparin (LMWH) versus heparin spray gel, Outcome 3 Allergic reaction or elevated sedimentation rate.

Comparison 17. High-dose unfractionated heparin (UFH) versus low-dose UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 1 Incidence of venous thromboembolism.

Study or subgroup	High-dose UFH n/N	Low-dose UFH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Marchiori 2002	1/30	6/30		0.17[0.02,1.3]
Favours high-dose UFH				Favours low-dose UFH

Analysis 17.2. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	High-dose UFH n/N	Low-dose UFH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Marchiori 2002	8/30	11/30		0.73[0.34,1.55]
Favours high-dose UFH				Favours low-dose UFH

Analysis 17.3. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 3 Major bleeding.

Study or subgroup	High-dose UFH n/N	Low-dose UFH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Marchiori 2002	0/30	0/30		Not estimable
Favours high-dose UFH				Favours low-dose UFH

Analysis 17.4. Comparison 17 High-dose unfractionated heparin (UFH) versus low-dose UFH, Outcome 4 Heparin-induced thrombocytopenia.

Study or subgroup	High-dose UFH n/N	Low-dose UFH n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Marchiori 2002	0/30	0/30		Not estimable

Favours high-dose UFH				Favours low-dose UFH

Comparison 18. Heparin calcium plus elastic compression bandage (ECB) versus ECB alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 Heparin calcium plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.

Study or subgroup	ECB + heparin calcium n/N	ECB n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1989	0/19	0/15		Not estimable

Favours ECB+heparin				Favours ECB

Comparison 19. Heparin subcutaneous (sc) versus defibrotide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in the analogue score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Adverse effects of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 19.1. Comparison 19 Heparin subcutaneous (sc) versus defibrotide, Outcome 1 Decrease in the analogue score.

Study or subgroup	Heparin sc		Defibrotide		Mean Difference		Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Belcaro 1990	20	6 (2)	20	3 (2)			3[1.76,4.24]
					Favours heparin sc		Favours defibrotide

Analysis 19.2. Comparison 19 Heparin subcutaneous (sc) versus defibrotide, Outcome 2 Adverse effects of treatment.

Study or subgroup	Heparin sc n/N	Defibrotide n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1990	0/20	0/20		Not estimable

Comparison 20. Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Major bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Heparin-induced thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 20.1. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 1 Venous thromboembolism.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	4/99	5/112		0.91[0.25,3.28]

Analysis 20.2. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	15/99	37/112		0.46[0.27,0.78]

Analysis 20.3. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 3 Major bleeding.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/99	0/112		Not estimable
Favours NSAIDs 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Analysis 20.4. Comparison 20 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 4 Heparin-induced thrombocytopenia.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Stenox Group 2003	0/99	0/112		Not estimable
Favours NSAIDs 0.1 0.2 0.5 1 2 5 10 Favours placebo				

Comparison 21. Indomethacin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 21.1. Comparison 21 Indomethacin versus placebo, Outcome 1 Adverse effects.

Study or subgroup	Indomethacin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Anonymous 1970	12/30	4/26		2.6[0.95,7.08]
Favours indomethacin 0.01 0.1 1 10 100 Favours placebo				

Comparison 22. Nimesulide versus diclofenac sodium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastric pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 22.1. Comparison 22 Nimesulide versus diclofenac sodium, Outcome 1 Gastric pain.

Study or subgroup	Nimesulide n/N	Diclofenac n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ferrari 1992	1/25	4/25		0.25[0.03,2.08]
Favours nimesulide 0.01 0.1 1 10 100 Favours diclofenac				

Comparison 23. Essaven gel versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 23.1. Comparison 23 Essaven gel versus placebo, Outcome 1 Intolerance.

Study or subgroup	Essaven gel n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Incandela 2001	0/16	0/14		Not estimable

Comparison 24. Thrombectomy plus venoruton plus elastic compression bandage (ECB) versus ECB alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 24.1. Comparison 24 Thrombectomy plus venoruton plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.

Study or subgroup	ECB + thromb + venoruton n/N	ECB n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1989	0/17	0/15		Not estimable

Comparison 25. Thrombectomy plus elastic compression bandage (ECB) versus ECB alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 25.1. Comparison 25 Thrombectomy plus elastic compression bandage (ECB) versus ECB alone, Outcome 1 Deep vein thrombosis.

Study or subgroup	ECB + thrombectomy n/N	ECB n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1989	0/14	0/15		Not estimable

Comparison 26. Ligation plus elastic compression stockings (ECS) versus ECS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 26.1. Comparison 26 Ligation plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.

Study or subgroup	ECS + ligation n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	2/78	6/78		0.33[0.07,1.6]

Analysis 26.2. Comparison 26 Ligation plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	ECS + ligation n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	6/78	13/78		0.46[0.18,1.15]

Comparison 27. Prophylactic unfractionated heparin (UFH) plus elastic compression stockings (ECS) versus ECS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 27.1. Comparison 27 Prophylactic unfractionated heparin (UFH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.

Analysis 27.2. Comparison 27 Prophylactic unfractionated heparin (UFH) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Comparison 28. Oral vasotonin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cured or substantially better	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Poor tolerability	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 28.1. Comparison 28 Oral vasotonin versus placebo, Outcome 1 Cured or substantially better.

Analysis 28.2. Comparison 28 Oral vasotonin versus placebo, Outcome 2 Poor tolerability.

Comparison 29. Elastic compression bandage (ECB) plus venoruton versus ECB alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep vein thrombosis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 29.1. Comparison 29 Elastic compression bandage (ECB) plus venoruton versus ECB alone, Outcome 1 Deep vein thrombosis.

Study or subgroup	ECB + venoruton n/N	ECB n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1989	0/18	0/15		Not estimable

Comparison 30. Oral heparansulphate versus oral sulodexide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Redness disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pain disappearance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Disappearance of itching	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Oedema improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Trophism improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 30.1. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 1 Redness disappearance.

Study or subgroup	Heparin sulphate n/N	Sulodexide n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Messa 1997	14/15	10/15		1.4[0.95,2.05]

Analysis 30.2. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 2 Pain disappearance.

Study or subgroup	Heparin sulphate n/N	Sulodexide n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Messa 1997	12/15	10/15		1.2[0.77,1.86]

Analysis 30.3. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 3 Disappearance of itching.

Analysis 30.4. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 4 Oedema improvement.

Analysis 30.5. Comparison 30 Oral heparansulphate versus oral sulodexide, Outcome 5 Trophism improvement.

Comparison 31. Oxyphenbutazone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tenderness improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 31.1. Comparison 31 Oxyphenbutazone versus placebo, Outcome 1 Tenderness improvement.

Comparison 32. Vitamin K antagonist (VKA) plus elastic compression stockings (ECS) versus ECS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 32.1. Comparison 32 Vitamin K antagonist (VKA) plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.

Study or subgroup	ECS + VKA n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	0/71	6/78		0.08[0.1,1.47]

Analysis 32.2. Comparison 32 Vitamin K antagonist (VKA) plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	ECS + VKA n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	5/71	13/78		0.42[0.16,1.13]

Comparison 33. Stripping plus elastic compression stockings (ECS) versus ECS alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Extension or recurrence (or both) of superficial thrombophlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 33.1. Comparison 33 Stripping plus elastic compression stockings (ECS) versus ECS alone, Outcome 1 Venous thromboembolism.

Study or subgroup	ECS + stripping n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	2/70	6/78		0.37[0.08,1.78]

Analysis 33.2. Comparison 33 Stripping plus elastic compression stockings (ECS) versus ECS alone, Outcome 2 Extension or recurrence (or both) of superficial thrombophlebitis.

Study or subgroup	ECS + stripping n/N	ECS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Belcaro 1999	1/70	13/78		0.09[0.01,0.64]

Comparison 34. Enzyme therapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Responders	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 34.1. Comparison 34 Enzyme therapy versus placebo, Outcome 1 Pain reduction.

Study or subgroup	Enzyme therapy		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Marshall 2001	74	3.6 (2.1)	74	2.6 (2.4)		1[0.28,1.72]

Analysis 34.2. Comparison 34 Enzyme therapy versus placebo, Outcome 2 Responders.

Study or subgroup	Enzyme therapy n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Marshall 2001	57/74	43/74		1.33[1.05,1.67]

Comparison 35. Desmin intramuscular (im) 200 versus desmin 100

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse drug reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 35.1. Comparison 35 Desmin intramuscular (im) 200 versus desmin 100, Outcome 1 Adverse events.

Study or subgroup	Desmin im 200 n/N	Desmin 100 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Andreozzi 1996	0/20	3/17		0.12[0.01,2.22]
Favours desmin 200 0.001 0.1 1 10 1000 Favours desmin 100				

Analysis 35.2. Comparison 35 Desmin intramuscular (im) 200 versus desmin 100, Outcome 2 Adverse drug reactions.

Study or subgroup	Desmin im 200 n/N	Desmin 100 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Andreozzi 1996	0/20	0/17		Not estimable
Favours desmin 200 0.1 0.2 0.5 1 2 5 10 Favours desmin 100				

Comparison 36. Desmin subcutaneous (sc) 2 × 100 versus desmin 100

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse drug reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 36.1. Comparison 36 Desmin subcutaneous (sc) 2 × 100 versus desmin 100, Outcome 1 Adverse events.

Study or subgroup	Desmin sc 2×100 n/N	Desmin 100 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Andreozzi 1996	1/18	3/17		0.31[0.04,2.74]
Favours desmin 200 0.01 0.1 1 10 100 Favours desmin 100				

Analysis 36.2. Comparison 36 Desmin subcutaneous (sc) 2 × 100 versus desmin 100, Outcome 2 Adverse drug reactions.

Study or subgroup	Desmin sc 2×100 n/N	Desmin 100 n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Andreozzi 1996	1/18	0/17		2.84[0.12,65.34]
Favours desmin 200 0.01 0.1 1 10 100 Favours desmin 100				

Comparison 37. Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (VAS, cm) at 3 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Skin erythema (cm ²) at 3 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 SF-36 physical score at 3 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 SF-36 mental score at 3 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 37.1. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 1 Pain (VAS, cm) at 3 weeks.

Study or subgroup	LMWH + ECS		LMWH		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Boehler 2014	39	0.8 (1.4)	41	0.9 (2.2)		-0.15[-0.95,0.65]
					Favours LMWH+ECS	Favours LMWH

Analysis 37.2. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 2 Skin erythema (cm²) at 3 weeks.

Study or subgroup	LMWH + ECS		LMWH		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Boehler 2014	39	13.9 (23.5)	41	20.4 (28.4)		-6.54[-17.94,4.86]
					Favours LMWH+ECS	Favours LMWH

Analysis 37.3. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 3 SF-36 physical score at 3 weeks.

Study or subgroup	LMWH + ECS		LMWH		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Boehler 2014	39	45.1 (8)	41	42.1 (10)		2.92[-1.04,6.88]
					Favours LMWH+ECS	Favours LMWH

Analysis 37.4. Comparison 37 Prophylactic low molecular weight heparin (LMWH) plus elastic compression stockings (ECS) versus prophylactic LMWH, Outcome 4 SF-36 mental score at 3 weeks.

Study or subgroup	LMWH + ECS		LMWH		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Boehler 2014	39	46.4 (9.3)	41	49.4 (10.4)	+	-2.98[-7.3,1.34]
					Favours LMWH+ECS	Favours LMWH

APPENDICES

Appendix 1. CENTRAL search strategy

Search run on Thur 9 Mar 2017		Hits
#1	MESH DESCRIPTOR Thrombophlebitis EXPLODE ALL TREES	1046
#2	MESH DESCRIPTOR Phlebitis	145
#3	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES WITH QUALIFIERS CO	197
#4	(superficial near thrombo*):TI,AB,KY	152
#5	(superficial near phleb*):TI,AB,KY	33
#6	SVT:TI,AB,KY	175
#7	*phleb*:TI,AB,KY	3102
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	3452
#9	* NOT SR-PVD:CC AND 12/12/2012 TO 28/02/2017:DL	349958
#10	#8 AND #9	707

Appendix 2. Trials registries searches

ClinicalTrials.gov

30 studies found for: thrombophlebitis

World Health Organization International Clinical Trials Registry Platform

136 records for 69 trials found for: thrombophlebitis AND leg

ISRCTN Register

30 results thrombophlebitis

FEEDBACK

Comment on data analysis, 12 February 2009

Summary

There are some analyses that are difficult to interpret and generate more statistics than data. This type of analysis is recommended in the Cochrane manual, but I am sure there must be a better way. See "Comparison 23. Exhirud ointment versus placebo". This has one study. One outcome "efficacy" was split into 4 categories, and there were thus 4 analyses for 'excellent/good/some/no efficacy'. (Analysis 23.2)

Reply

We fully agree with these comments, however, we felt that reporting these analysis in the dedicated section seemed the only way to inform the reader about these outcomes while avoiding to increase the confusion of the Results section caused by the already long list of comparisons as well as the endless list of studies cited after any statement. We welcome any advice.

Contributors

Feedback: Michael Power, Guideline author

Reply: Marcello Di Nisio, Iris M Wichers, Saskia Middeldorp

Comment on Belcaro papers, 13 February 2009

Summary

This review includes a number of papers by Gianni Belcaro who was erased from the UK medical register in June 2007. This was for "misconduct", which seems to have been that he included as co-authors on his papers people who were not involved in the research. The GMC report does not suggest that data was falsified. <http://webcache.gmc-uk.org/minutesfiles/3313.HTML>
Should you mention in the systematic reviews that the data may be suspect in Belcaro's papers?

Reply

We understand and share the suspicion on the reliability of the data. However, it does not seem that the reason for misconduct would influence the quality of the data which, in any case, the GMC report suggested not to be falsified. Therefore we do not think that this misconduct should be explicitly mentioned in the text. Moreover, the data from the studies of Belcaro do not affect the main conclusions of the review. Finally the significant methodological limitations of these studies are underlined in the text.

Contributors

Feedback: Michael Power, Guideline author

Reply: Marcello Di Nisio, Iris M Wichers, Saskia Middeldorp

Best therapeutic options for ST of the legs, 27 October 2010

Summary

The authors concluded that 'low molecular weight heparin and NSAIDs appear as the current best therapeutic options for ST of the legs.' This statement does not fully capture the data presented in the review.

In their discussion section the authors note several serious limitations in the studies presented in the review. These include unclear methods of allocation or randomisation, lack of a placebo group as control, high drop out rates, and poor reporting of serious adverse events. In addition, study data could not be pooled due to a high level of heterogeneity and thus data remains underpowered to show any difference in VTE between treatment groups.

In the implications for practice section the authors concede that "the data are still too preliminary to make any recommendation". Yet the authors proceed to state that one month of therapy with LMWH may be appropriate to prevent VTE events as well the extension and/or recurrence of ST. Given these drawbacks coupled with the fact that individual trials fail to show significant differences between treatment groups, a final conclusion should not be drawn regarding therapeutic options.

Perhaps the question that should be asked is not what the best treatment for ST is, but rather whether or not ST requires treatment at all. The authors note that ST is estimated to be more common than DVT and go on to say that ST is associated with DVT in 6 to 44% of patients, but this does nothing to answer the question of how prevalent ST is in the general population. Given that limited data is available on the prevalence of ST and its clinically relevant outcomes, it is not clear to us whether or not treatment of ST is required to improve patient outcomes.

Reply

We agree with these comments and have modified the text accordingly. Since our previous review, the CALISTO study has been published ([Decousus 2010b](#)). The results of this large and methodologically robust RCT provide good answers to some of the reviewer's concerns.

Contributors

Feedback: Michelle Co, BScPharm; Hayley Coe, BScPharm; Sarah West, BSc, BScPharm; Aaron Tejani BScPharm, PharmD

Reply: Marcello Di Nisio, Iris M Wichers, Saskia Middeldorp

WHAT'S NEW

Date	Event	Description
9 March 2017	New search has been performed	Searches re-run. Three new trials included and three trials excluded. Ten additional publications to previously included studies.
9 March 2017	New citation required but conclusions have not changed	Searches re-run. Three new trials included and three trials excluded. Ten additional publications to previously included studies. Review updated including the addition of Summary of Findings tables. Conclusions not changed.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 1, 2007

Date	Event	Description
15 October 2013	Amended	Amendments made to the 'Risk of bias' tables and minor data errors corrected. Outcomes reordered to reflect clinical importance.
23 November 2012	New search has been performed	Searches re-run. Four new trials included and one new trial excluded. Conclusions unchanged.
23 November 2012	New citation required but conclusions have not changed	Review updated. Four new trials included and one new trial excluded. Conclusions unchanged.
30 November 2011	Feedback has been incorporated	Feedback addressed.
30 November 2011	New search has been performed	Review updated, searches rerun. Two new trials included, one being a large RCT with fondaparinux.
30 November 2011	New citation required and conclusions have changed	Review updated. Conclusions changed.
27 October 2010	Feedback has been incorporated	Feedback added
26 April 2010	Amended	Contact details updated
1 September 2008	Amended	Converted to new review format.

Date	Event	Description
19 February 2007	New citation required and minor changes	Updated to correct error in citation. Searches re-run and no new trials found.

CONTRIBUTIONS OF AUTHORS

MDN: selected and assessed the quality of trials, extracted data, and wrote the review.

IW: selected and assessed the quality of trials, extracted data, and commented on the review.

SM: supervised the development of the review in all its phases.

DECLARATIONS OF INTEREST

MDN: Dr Di Nisio reported participation to Advisory Boards for Daiichi-Sankyo and Pfizer, and receiving consultancy fees from Daiichi-Sankyo and Bayer Health Care.

IW: none known.

SM: Dr Middeldorp was a member of the Steering Committee of the CALISTO study, which was funded by GlaxoSmithKline (GSK) and which investigated the efficacy and safety of fondaparinux for superficial thrombophlebitis; funds were paid to Dr Middeldorp's institution. Dr Middeldorp's institution had also received funding from several pharmaceutical companies, including GSK, BMS, Bayer, Boehringer Ingelheim, Sanofi, and Pfizer to support some of her other educational and research activities. The first version of this review was written before the CALISTO study was designed.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to evaluate publication bias using funnel plots and heterogeneity of treatment effects between trials using the Chi² test and the I² statistic. However, despite the relatively broad number of comparisons found, no funnel plots or tests of heterogeneity were performed since most studies did not evaluate the same treatment comparisons on the same study outcomes. For the same reason, subgroup analysis and sensitivity analysis to take into account possible sources of bias (e.g. open-label design, incomplete follow-up, high levels of exclusions unbalanced between the groups, or inadequate allocation concealment) were not possible. For most of the treatment comparisons, standardised mean differences (SMD) could not be calculated for continuous variables since the standard deviations of the means were not reported.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Anticoagulants [*therapeutic use]; Factor Xa Inhibitors [therapeutic use]; Fondaparinux; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight [*therapeutic use]; Polysaccharides [therapeutic use]; Randomized Controlled Trials as Topic; Rivaroxaban [therapeutic use]; Stockings, Compression; Thrombectomy; Thromboembolism [prevention & control]; Thrombophlebitis [drug therapy] [surgery] [*therapy]; Venous Thromboembolism [*prevention & control]

MeSH check words

Humans