Appendix S1. Search strategy

CINAHL (EBSCO)

S1 .(MH "Cerebrovascular Disorders+") or (MH "stroke patients") or (MH "stroke units")

S2 .TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)

S3 .TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)

S4 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)

S5 .S3 and S4

S6 .TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)

S7 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)

S8 .S6 and S7

S9 .S1 or S2 or S5 or S8

S10 .(MH "Thrombosis") or (MH "thromboembolism") or (MH "venous thrombosis") or (MH "venous thromboembolism")or (MH "thrombophlebitis")

S11 .TI thrombophlebit* or AB thrombophlebit*

S12 .TI venous N5 thrombo* or AB venous N5 thrombo*

S13 .TI vein N5 thrombo* or AB vein N5 thrombo*

S14 .TI (DVT OR VTE) or AB (DVT OR VTE)

S15 .TI thromboprophylaxis or AB thromboprophylaxis

S16 .TI phlebothrombosis or AB phlebothrombosis

S17 .MH "pulmonary embolism"

S18 .MH "pulmonary artery" and MH "embolism"

S19 .TI (pulmonary or lung) or AB (pulmonary or lung)

S20 .TI (embol* or thrombo* or infarct*) or AB (embol* or thrombo* or infarct*)

S21 .S19 and S20

S22 .S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S21

S23 .S9 AND S22

S24 .PT randomized controlled trial or clinical trial

S25 .(MH "Random Assignment") or (MH "Random Sample+")

S26 .(MH "Crossover Design") or (MH "Clinical Trials+")

S27 .(MH "Control (Research)") or (MH "Control Group")

S28 .(MH "Factorial Design") or (MH "Quasi-Experimental Studies") or (MH "Nonrandomized Trials")

S29 .(MH "Placebo Effect") or (MH "Placebos") or (MH "Meta Analysis")

S30 .(MH "Clinical Research") or (MH "Clinical Nursing Research")

S31 .(MH "Community Trials") or (MH "Experimental Studies or (MH "Study Design")

S32 .PT systematic review

S33 .TI (random* or RCT or RCTs) or AB (random* or RCT or RCTs)

S34 .TI (singl* or doubl* or tripl* or trebl*) or AB (singl* or doubl* or tripl* or trebl*)

S35 .TI (blind* or mask*) or AB (blind* or mask*)

S36 .S34 and S35

S37 .TI (crossover or cross-over or placebo* or controls or factorial or sham or assign* or allocat*) or AB (crossover or cross-over or placebo* or controls or factorial or sham or assign* or allocat*)

S38 .TI (clin* or control* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or control* or intervention* or compar* or experiment* or preventive or therapeutic)

S39 .TI trial*

S40 .S38 and S39

S41 .TI (meta analysis* or metaanalysis or meta-analysis or systematic review*) or AB (meta analysis* or metaanalysis or meta-analysis or systematic review*)

S42 .PT meta analysis

S43 .AB cochrane or medline or pubmed or embase or cinahl or cinhal or science citation index or reference list* or bibliograph* or hand-search* or handsearch* or relevant journals or manual search*

S44 .S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S36 OR S37 OR S40 OR S41 OR S42 OR S43

S45 .S23 AND S44

.Appendix S2

Figure 1.1 Effect of thigh-length GCS on death or dependency at six months

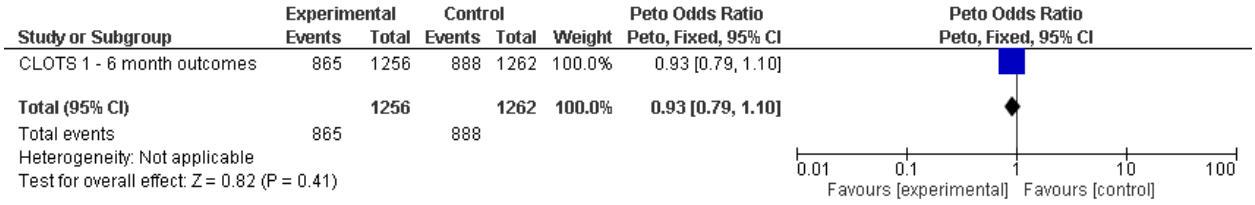


Figure 1.2 Effect of thigh-length GCS on death within the treatment period

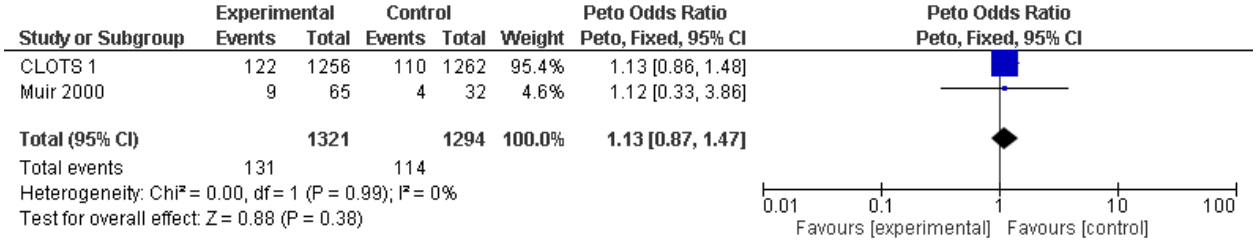


Figure 1.3 Effect of thigh-length GCS on any PE during treatment period

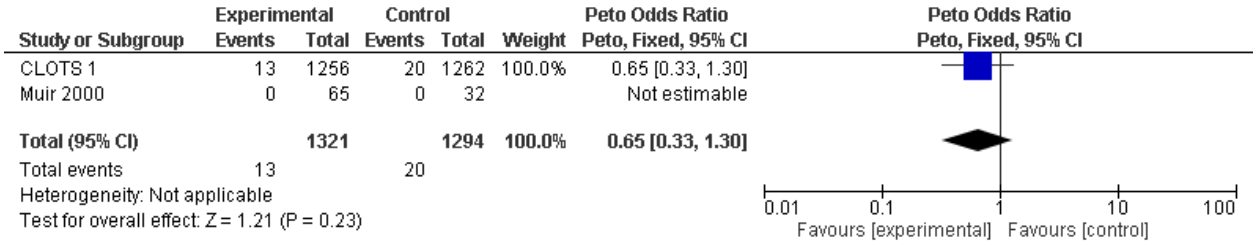


Figure 1.4 Effect of thigh-length GCS on any DVT during treatment period

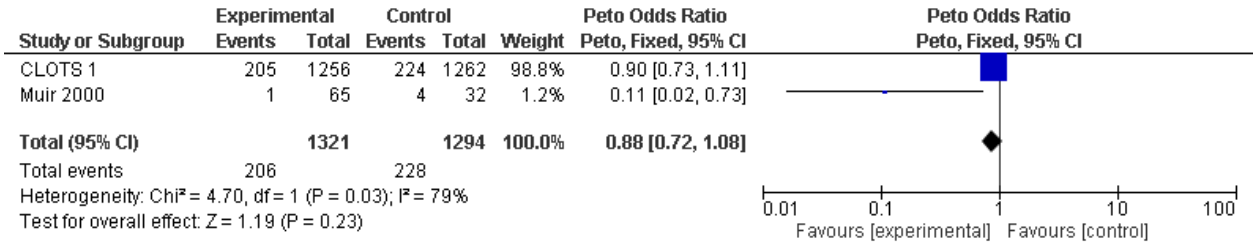


Figure 1.5 Effect of thigh-length GCS on skin breaks during treatment period

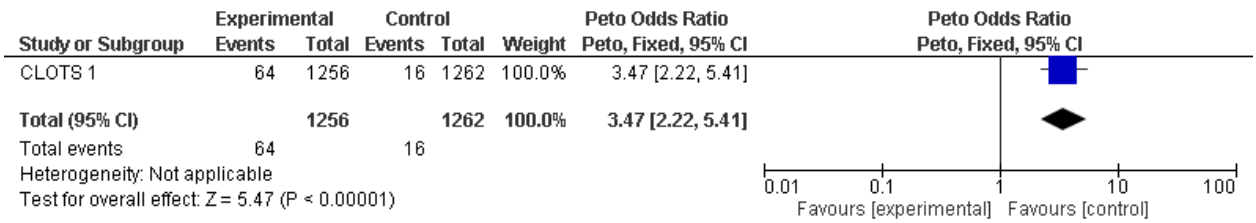


Figure 2.1 The effect of IPC on death or dependency at final follow up

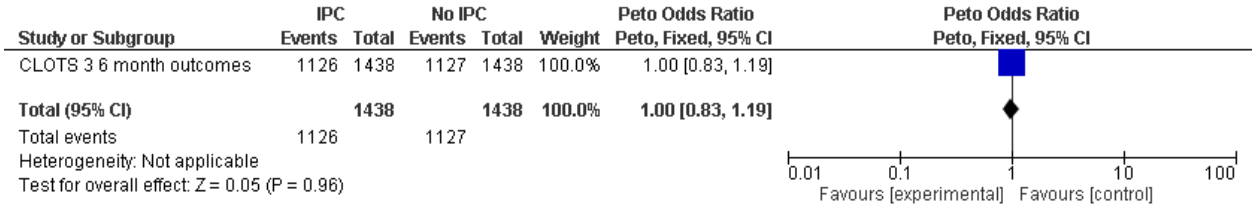


Figure 2.2 The effect of IPC on death within the treatment period

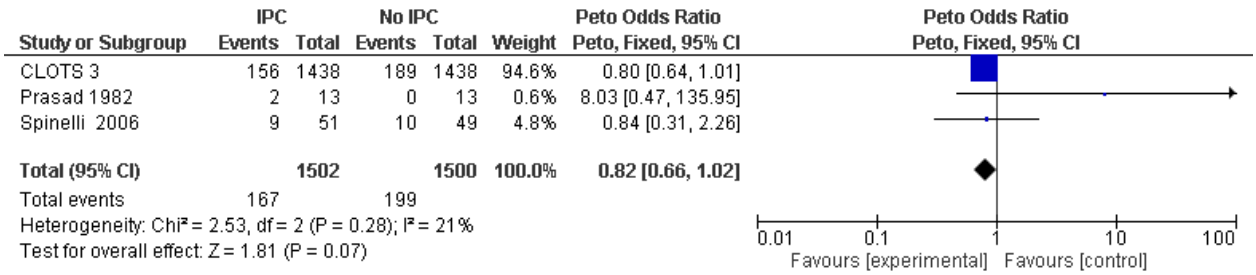


Figure 2.3 The effect of IPC on PE during treatment period

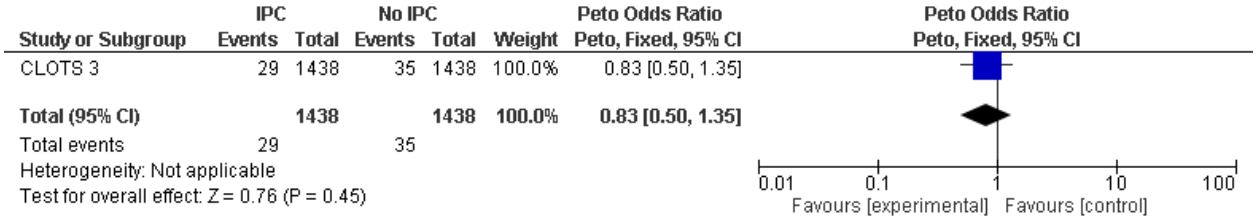


Figure 2.4 The effect of IPC on symptomatic DVT during treatment period

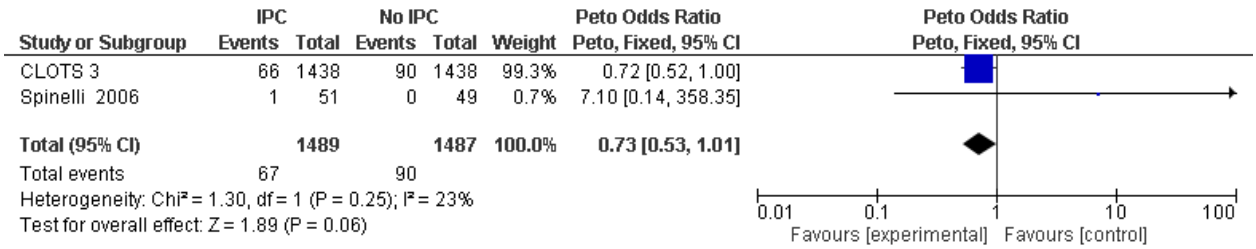


Figure 2.5 The effect of IPC on any DVT (including asymptomatic)

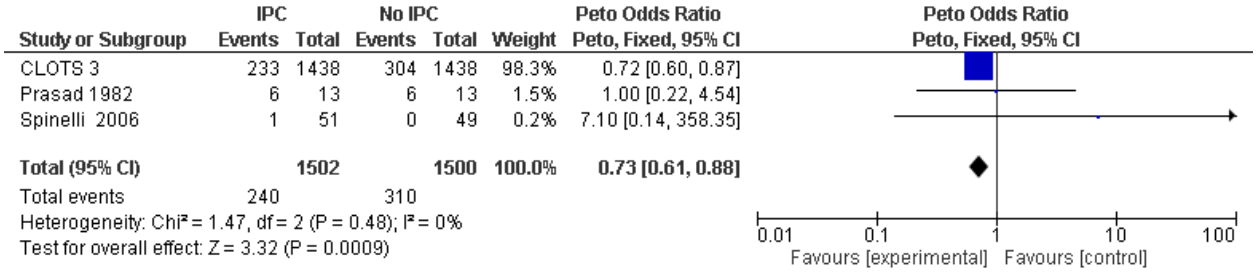


Figure 2.6 The effect of IPC on skin breaks during treatment period

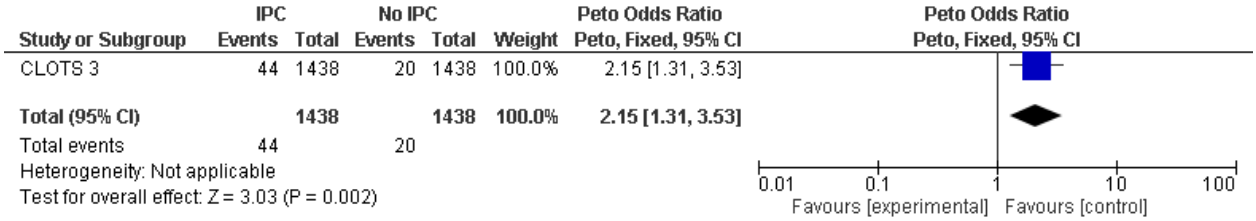


Figure 3.1 The effect on prophylactic anticoagulants of death or dependency at final follow up

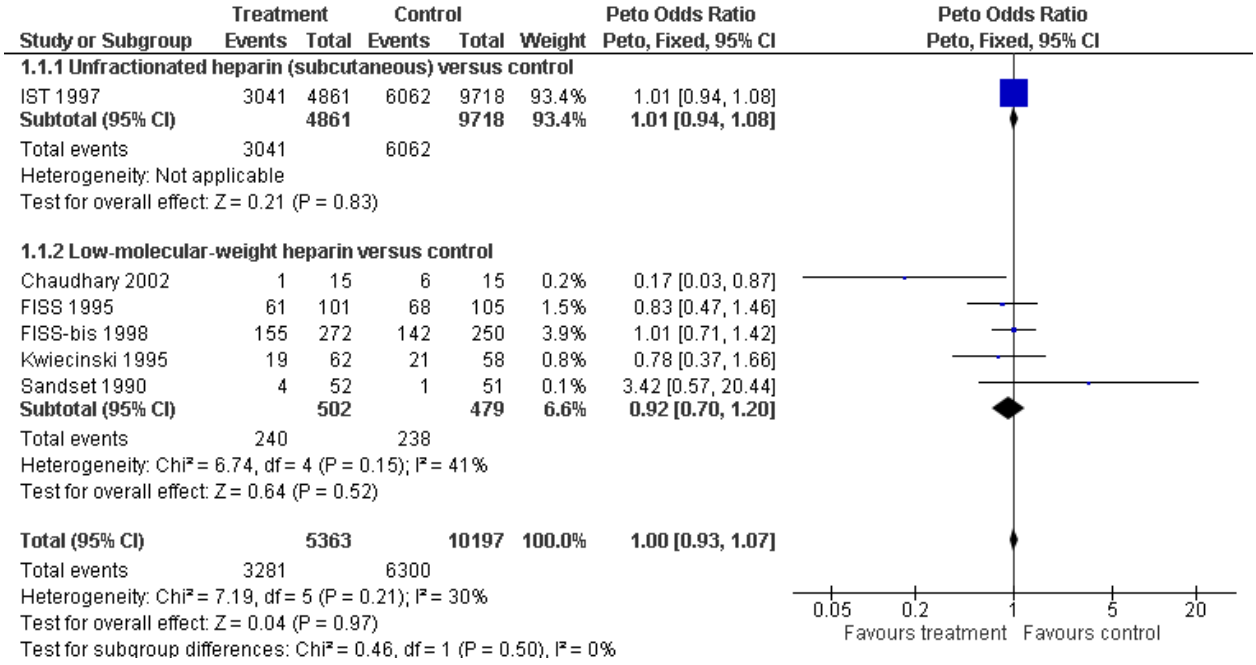


Figure 3.2 The effect of prophylactic anticoagulants on death during treatment

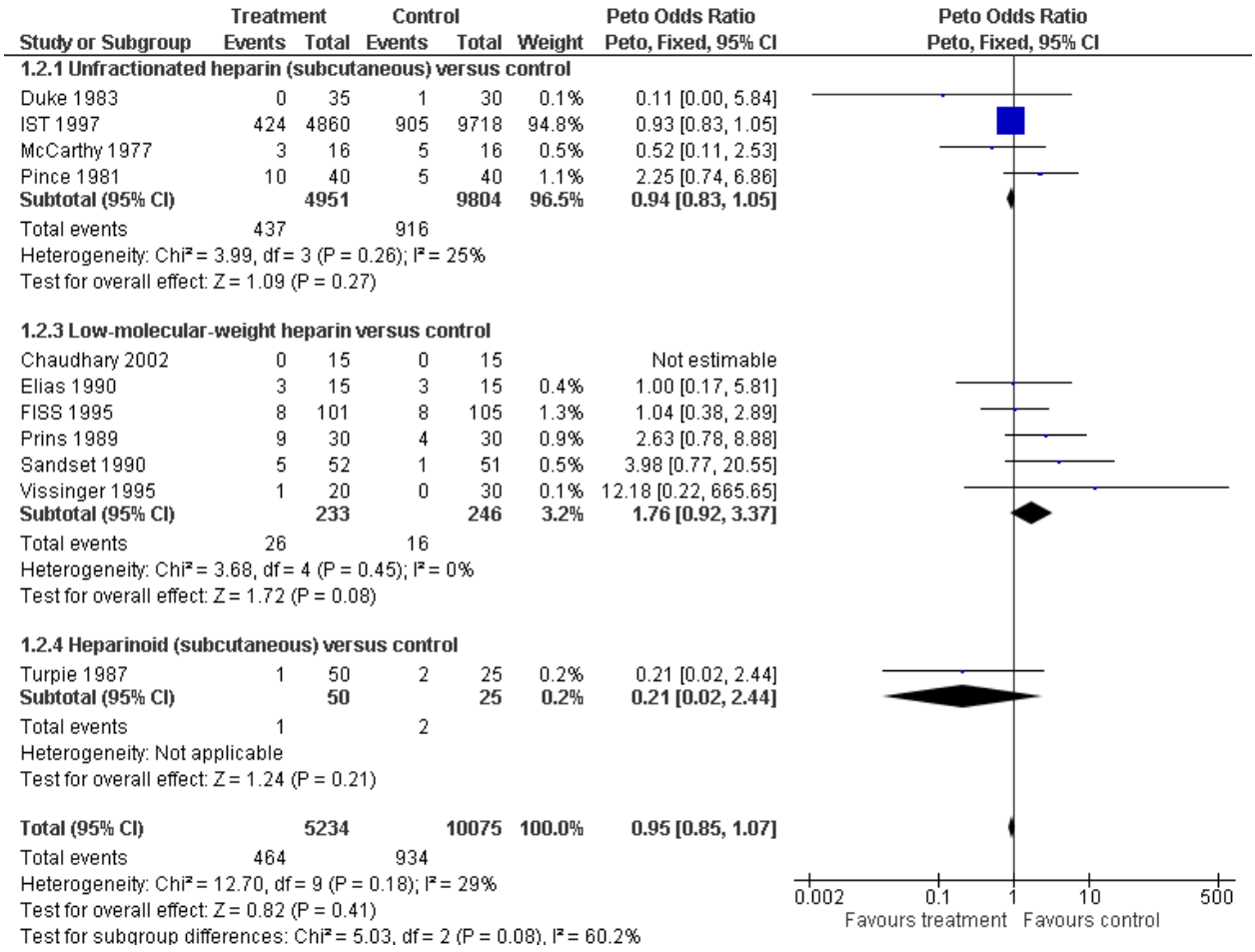


Figure 3.3 The effect of prophylactic anticoagulation on symptomatic intracranial bleeding during treatment period

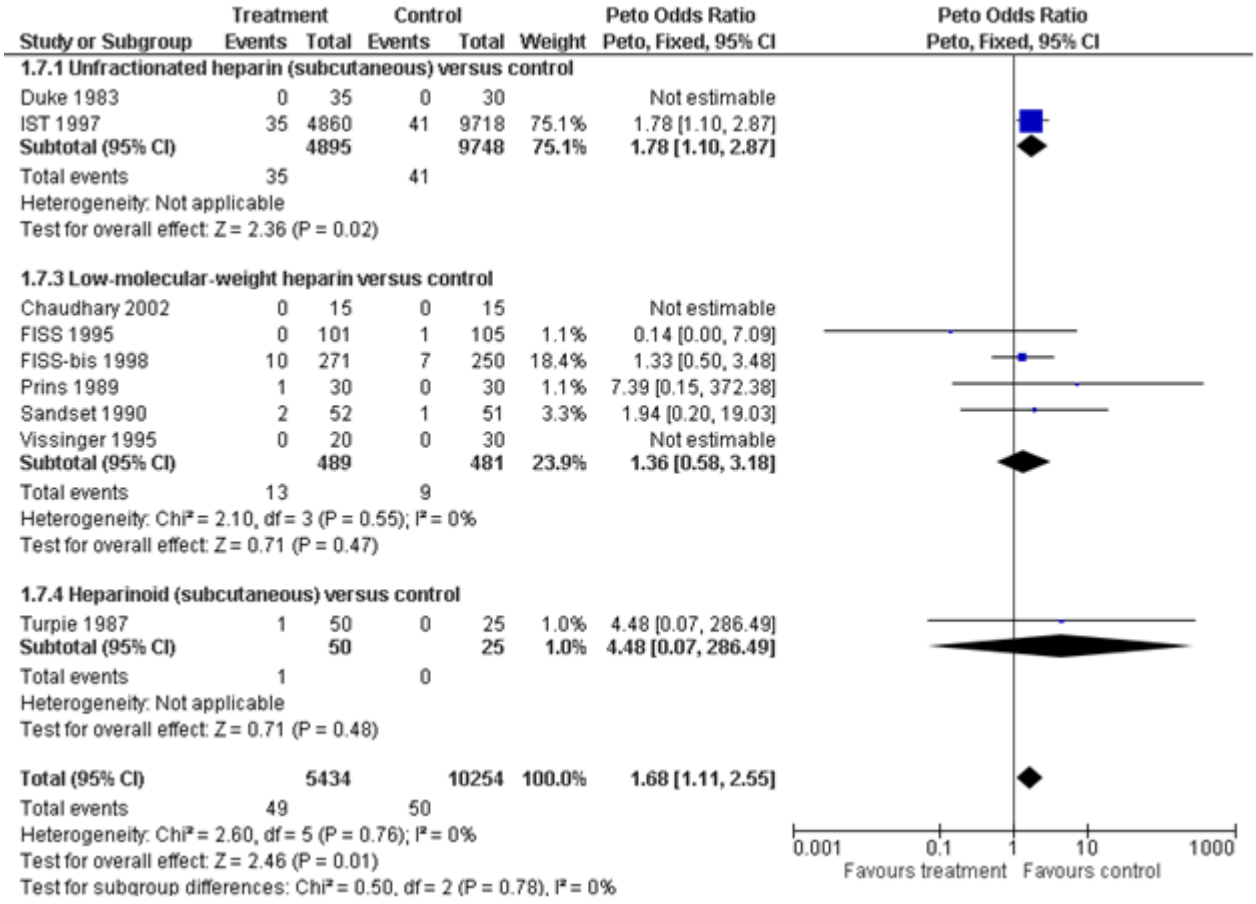


Figure 3.4 The effect on prophylactic anticoagulants on PE during treatment

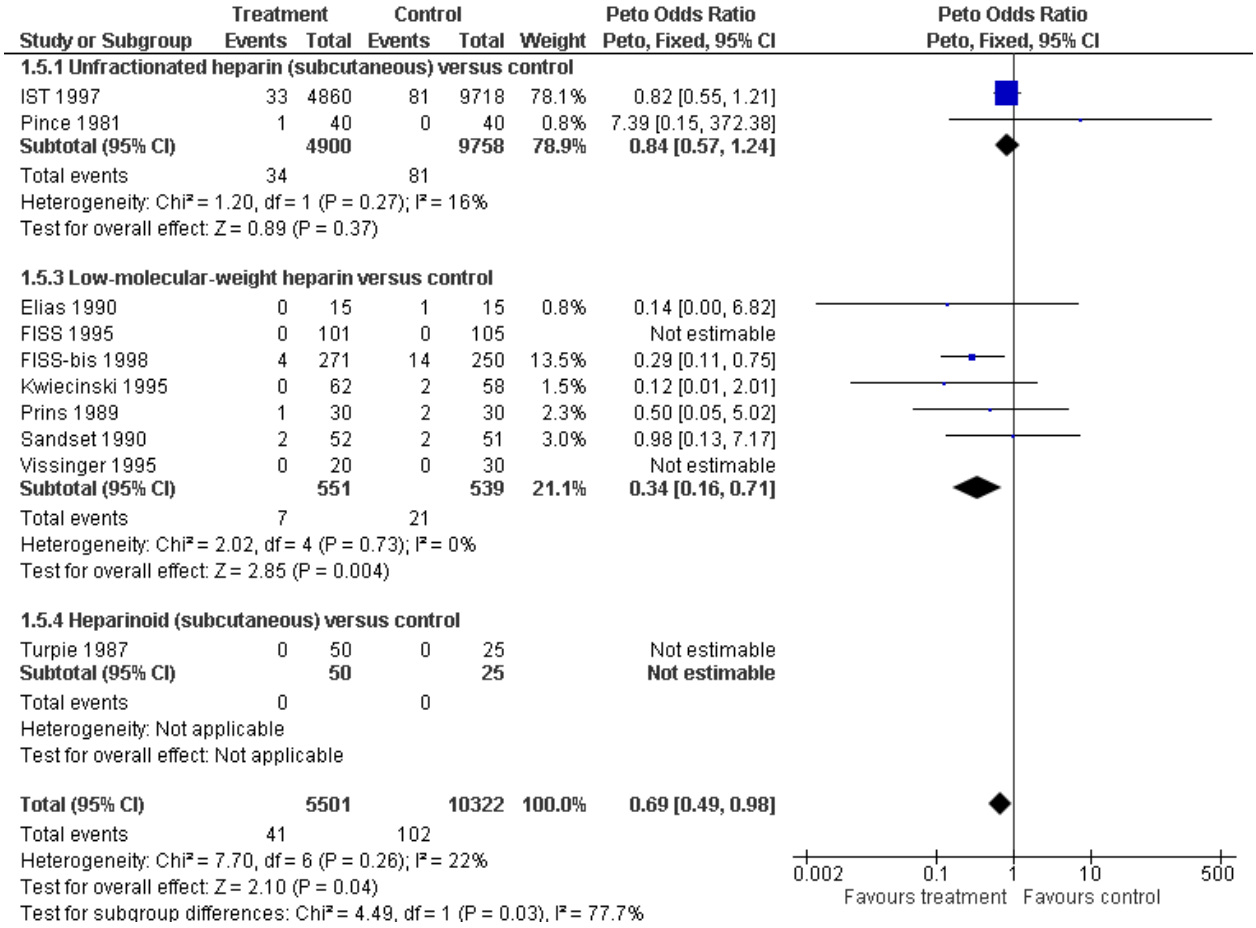


Figure 3.5 The effect of prophylactic anticoagulation on symptomatic extracranial bleeding during treatment period

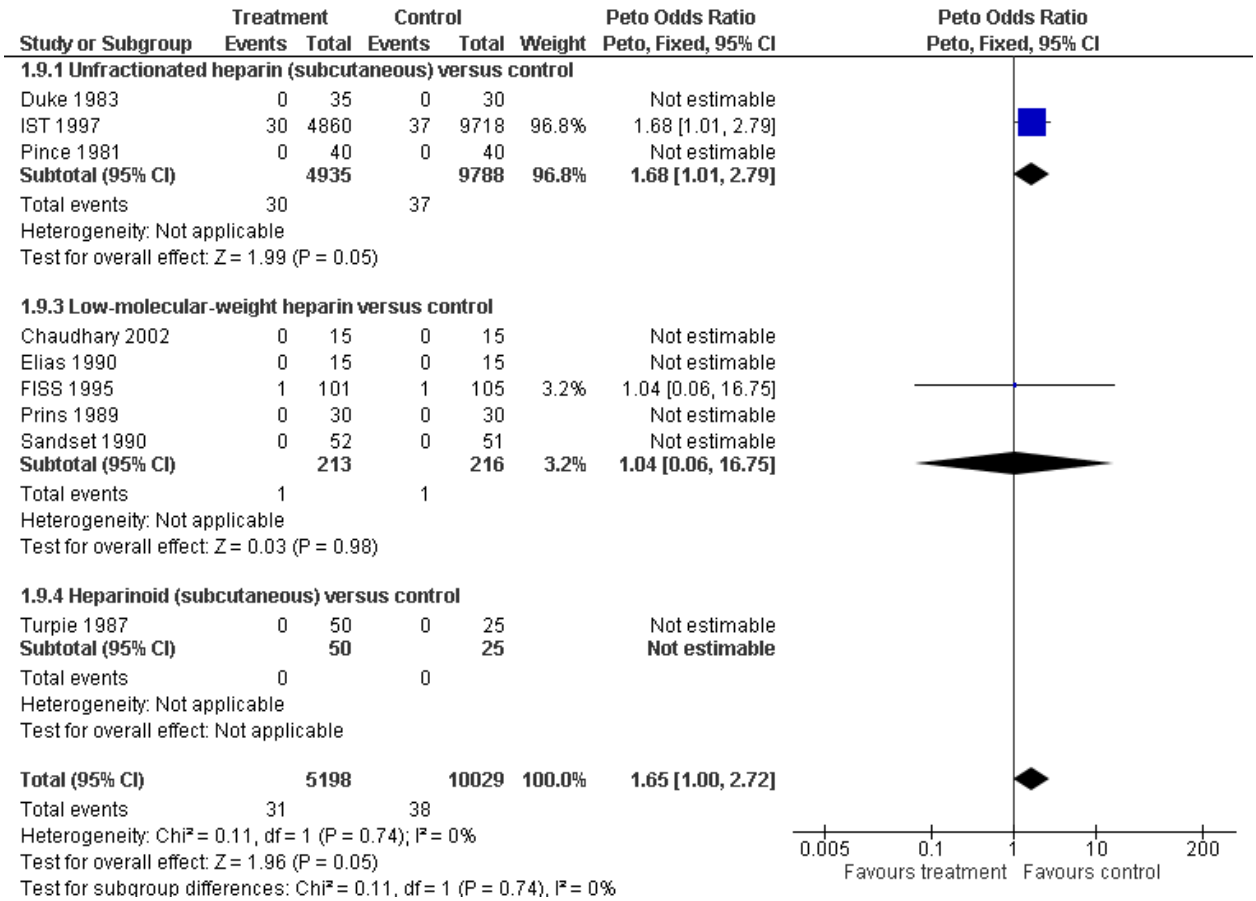


Figure 3.6 The effect on prophylactic anticoagulants on any DVT (including Isotope scanning) only during treatment

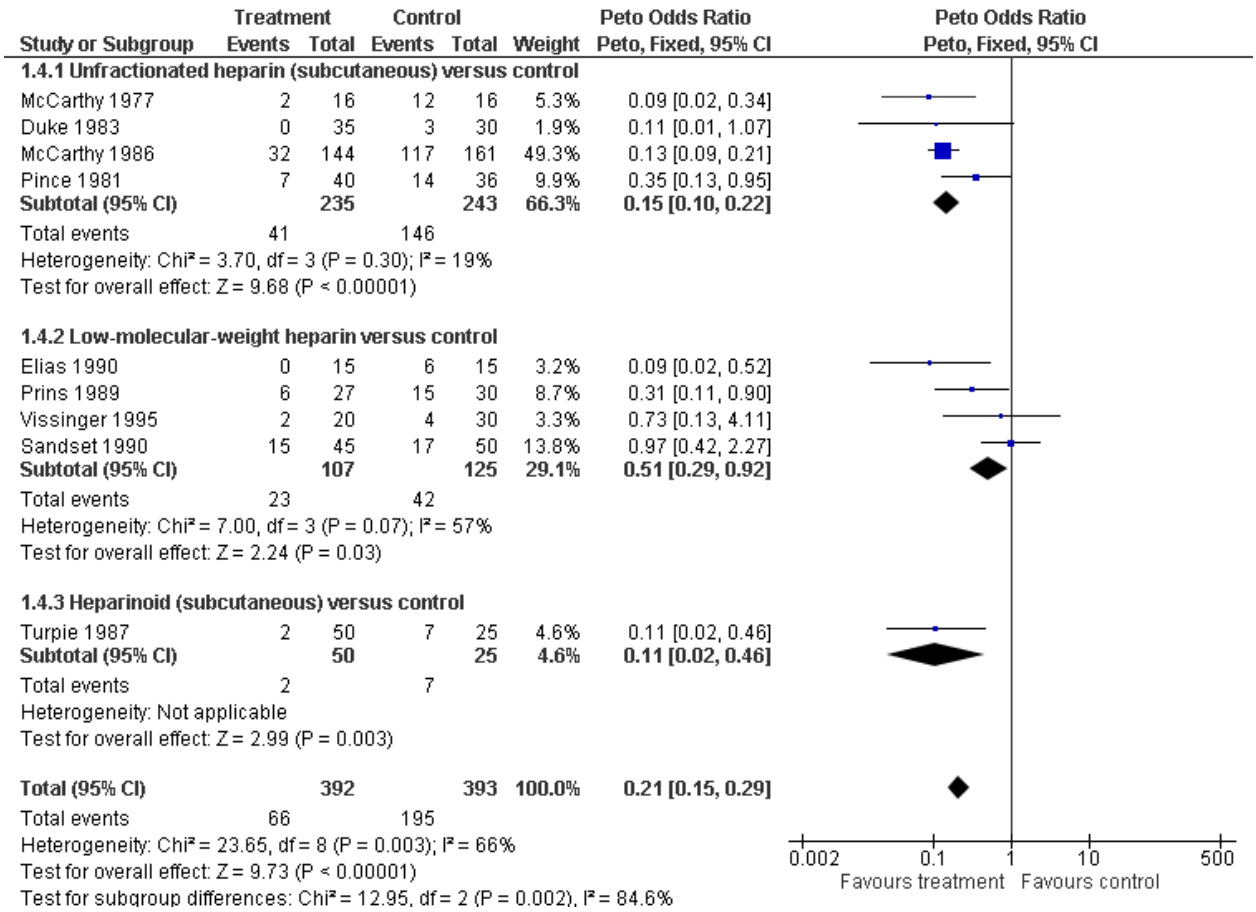


Figure 4.1 The effect of LMWH compared with unfractionated heparin on Death or dependency at final follow up

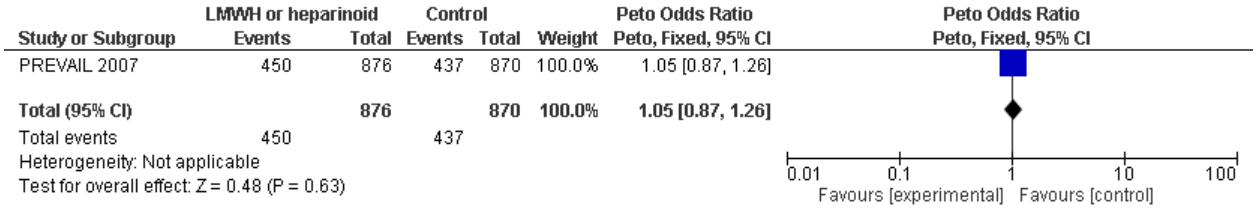


Figure 4.2 The effect of LMWH compared with unfractionated heparin on Death from all causes during follow up

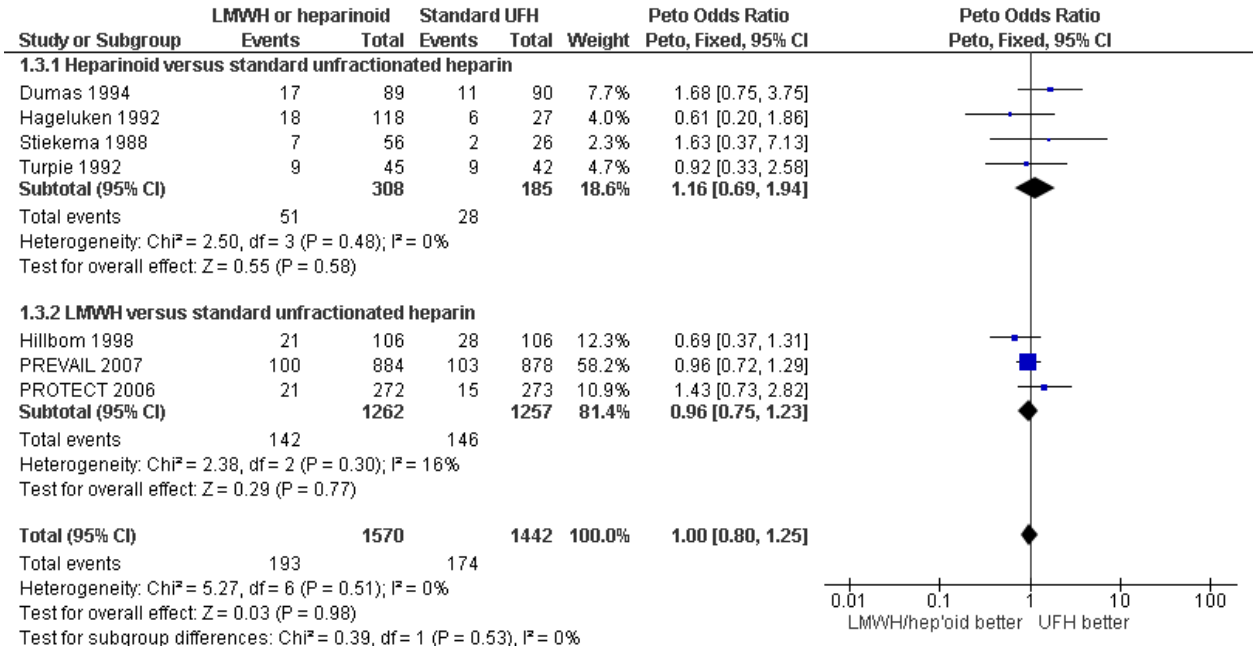


Figure 4.3 The effect of LMWH compared with unfractionated heparin on Symptomatic intracranial bleeding

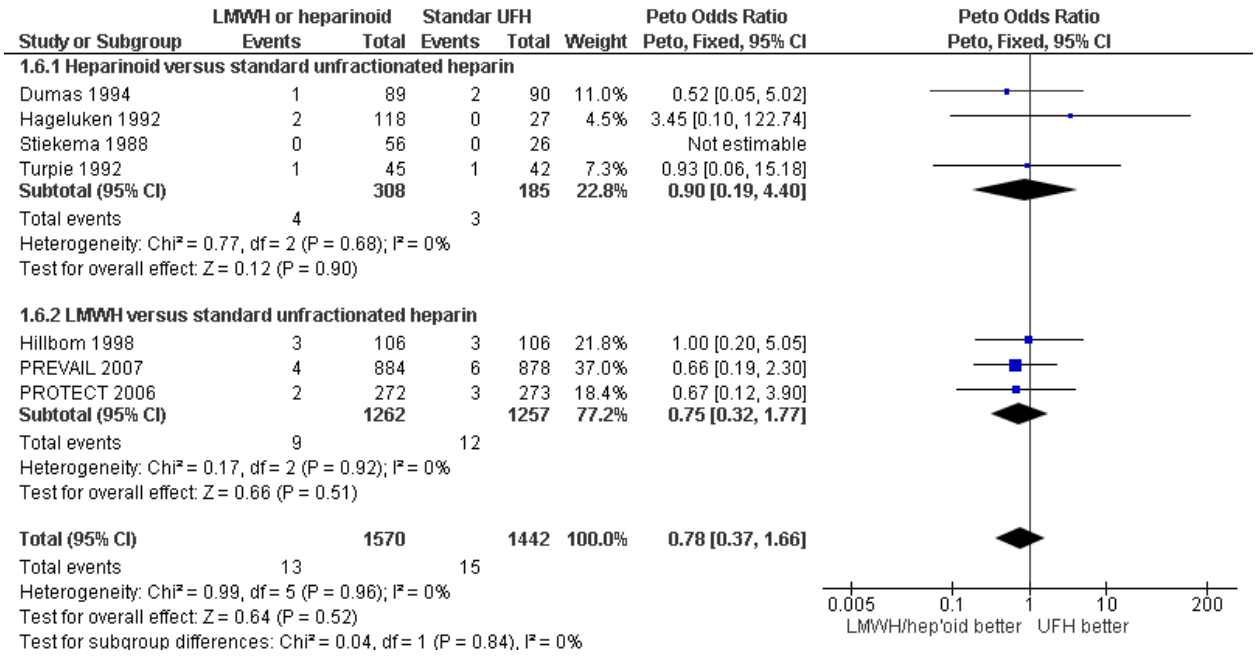


Figure 4.4 The effect of LMWH compared with unfractionated heparin on Pulmonary emboli

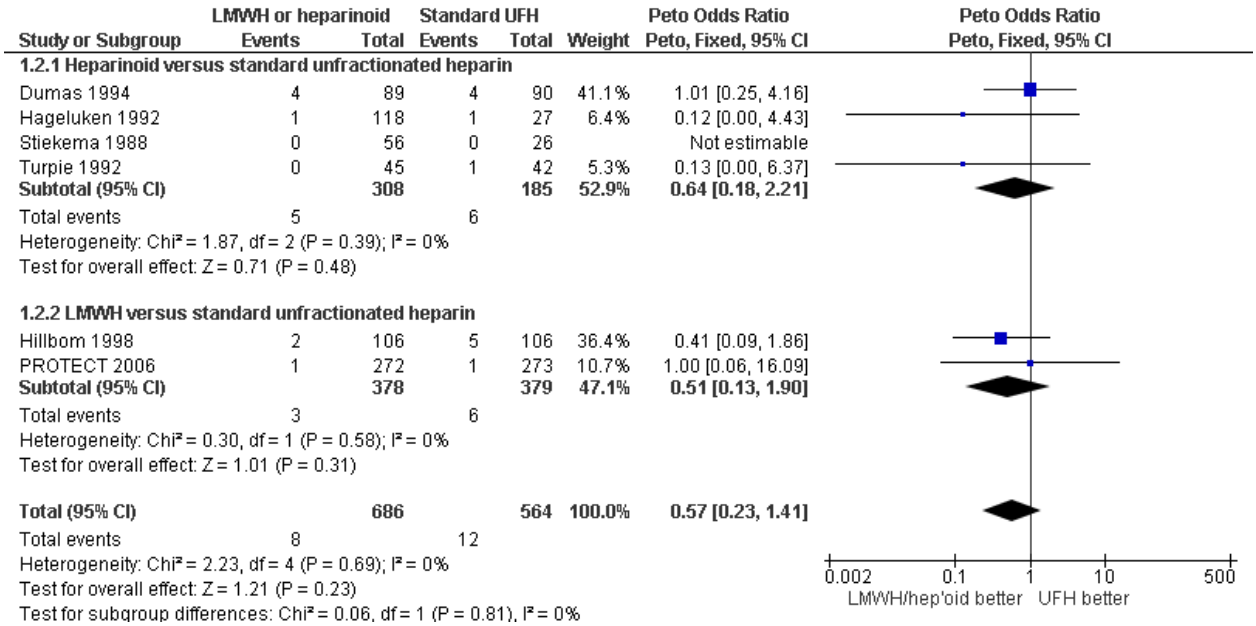


Figure 4.5 The effect of LMWH compared with unfractionated heparin on Extracranial bleeding

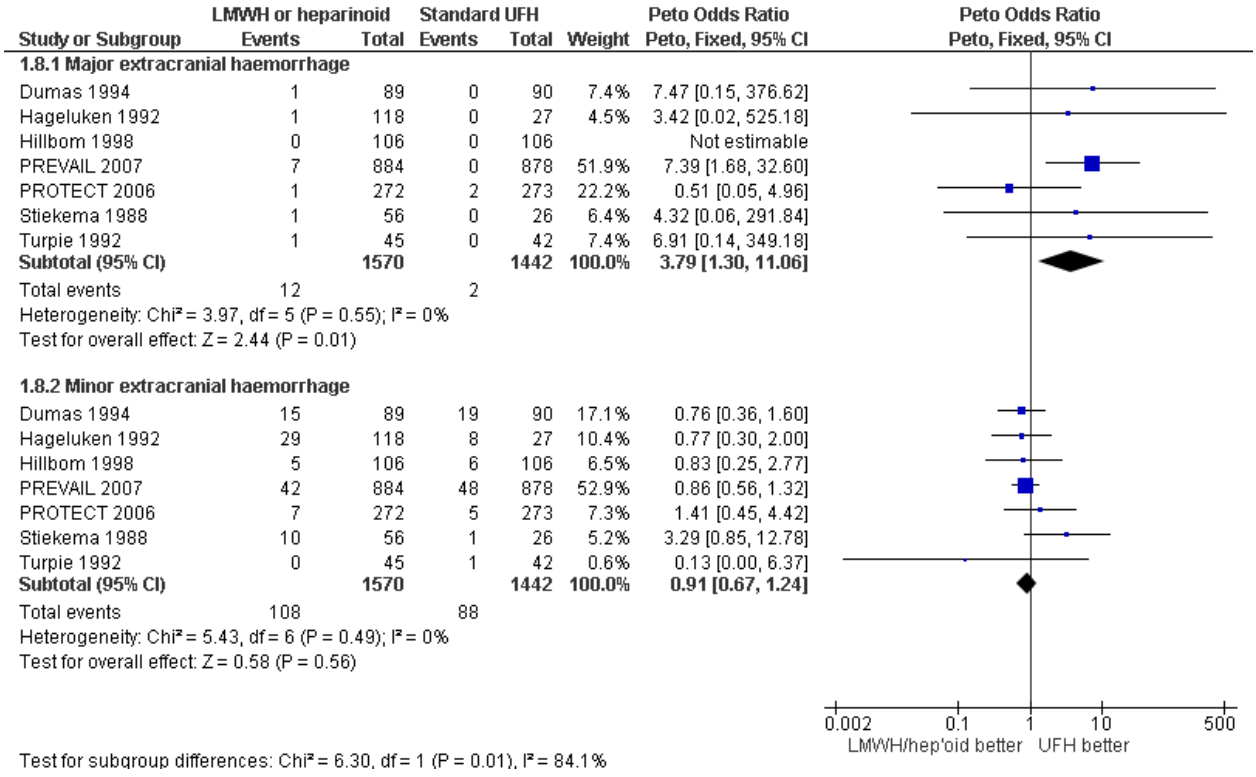
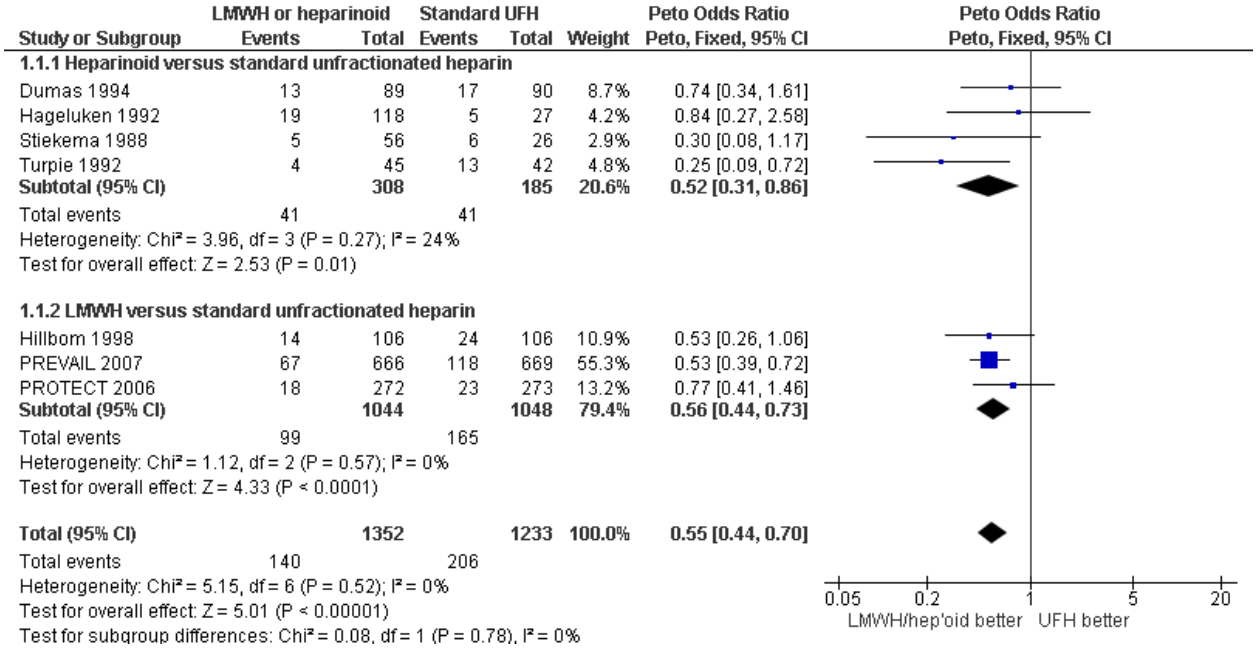


Figure 4.6 The effect of LMWH compared with unfractionated heparin on DVT during follow up



Evidence tables

Graduated Compression Stockings

Summary of included RCTs

Study reference (name)	CLOTS 1; Dennis (2009)
Methods	**Multicentre RCT (105 centres in UK with 6 month follow up**
Participants or study population	2518 Immobile stroke patients admitted to hospital within 7 days of the stroke and enrolled within 3 days of admission. Losses to follow up: 69 missing data (41 in treatment group and 28 in control group) - no CDU prior to death or 30 days DVT diagnosis: CDU (minimum of the popliteal and femoral veins) between day 7 and 10 and between day 25 and 30 Statistical analysis: odds ratio and NNT Scheduled treatment and follow-up period: 30 days; clinical follow up at 6 months Age: 76 years (68 to 83) for both groups Sex: males 49.4% (620/1256) in the treatment group and 49.3% in the control group (622/1262) Exclusion criteria: peripheral vascular disease, or with diabetic/sensory neuropathy, if clinicians judged GCS could cause skin damage Full intention-to-treat analysis: performed
Intervention & comparator	Interventions Type: thigh-length Tyco Healthcare TED GCS Control: 1262, Treatment: 1256 Duration applied: night and day until death/discharge/mobile/refused Use of anticoagulants post randomisation: group allocated GCS • 117 post-randomisation prophylactic dose heparin/LMWH prescribed • 78 post-randomisation treatment dose heparin/LMWH prescribed • 186 post-randomisation warfarin prescribed Use of anticoagulants post randomisation: group allocated 'avoid GCS' • 129 post-randomisation prophylactic dose heparin/LMWH prescribed • 97 post-randomisation treatment dose heparin/LMWH prescribed • 208 post-randomisation warfarin prescribed
Outcomes	• All cause mortality • Disability at 6 month measured with Oxford handicap scale • Pulmonary embolism (confirmed by imaging or autopsy) up to six months • Symptomatic DVT (proximal only and combined distal or proximal) – confirmed mainly with compression duplex ultrasound within 6 months • Skin breaks within 30days • Asymptomatic DVT (proximal only and combined distal or

	proximal) within 30 days
Notes	The primary outcome focused on proximal DVTs (popliteal or femoral) rather than any DVT. Randomising clinicians were allowed to elect prior to randomisation whether patients would have a second CDU at 25 to 30 days. . The median delay from stroke onset to enrolment was 2 days but there was no trend towards more effect with earlier recruitment

Study: CLOTS 1	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to examine mortality
Quality of evidence	**Moderate**
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to look at disability
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to look at PE
Quality of evidence	**Moderate**
	Outcome: Symptomatic DVT
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to look at symptomatic DVT
Quality of evidence	**Moderate**
	Outcome: Skin breaks
Bias	Very Serious – based on casenote review by unblended person
Indirectness	Serious – little indication of whether breaks associated with IPC
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	No serious – mostly asymptomatic , based on blinded imaging
Indirectness	No serious
Inconsistency	Serious – I2=79% p=0.03, with Muir 2000
Imprecision	No serious
Quality of evidence	**Moderate**

Study reference (name)	**Muir 2000**
Methods	Single centre RCT in UK Computer generated random numbers in sealed envelopes Exclusion to post-randomisation: 1 Losses to follow up: 19 DVT diagnosis: CDU at enrolment and at day 7 ± 2 Statistical analysis: odds ratio and NNT Scheduled treatment and follow-up period 7 ± 2 days

Participants or study population	Total number of participants: 98 (1 missing data) Total available for analysis: 71 Age: mean age > 73 years Immobilisation: yes Inclusion criteria: acute stroke within 24 hours Exclusion criteria: patients with coma, life-threatening inter-current illness, critical lower limb ischaemia or severe dermatological conditions Full intention-to-treat analysis was not performed
Intervention & comparator	Interventions Type: GCS thigh-length Kendall TED or Brevett TX brands Control: 32 Treatment: TED group 37, TX group 28 Duration applied: time of application and duration applied till follow up Compression duplex ultrasound on Day 9
Outcomes	Mortality by Stocking: 9/65, Control 4/32 by Day 9 Pulmonary embolism – none by day 9 Symptomatic DVT – 1 but group not stated DVT detected on compression duplex ultrasound – all but one was asymptomatic Stockings: 7/65, Control: 7/32 – but some were present prior to randomisation. Only 1/65 and 4/32 occurred after treatment
Notes	Notes TX and TED groups were combined for analysis of efficacy. Some data reported in the results do not correspond to data reported in tables Did not report if ischaemic or haemorrhagic strokes

Study: Muir 2000	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Very serious – very small numbers
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	Serious – lots of patients excluded from analyses because had DVT at baseline
Indirectness	No serious
Inconsistency	Serious – I^2=79% p=0.03, with CLOTS 1
Imprecision	Serious – very small numbers
Quality of evidence	**Low**

Intermittent Pneumatic Compression

Included RCTs

Study reference (name)	CLOTS 3; Dennis (2013) Dennis (2014)
Methods	**Multicentre RCT (105 centres in UK with 6 month follow up** Central web based minimisation system Blinding described: blinded assessment of primary outcome and

<table>
<tr><td></td><td>six month outcomes but not secondary outcomes at 30 days (fractures, skins breaks, symptomatic DVT, PE</td></tr>
<tr><td>Participants or study population</td><td>2876 Immobile stroke patients admitted to hospital within 3 days of the stroke and enrolled within 3 days of admission.
Mean age: 74yrs;
Attrition:
Loss for primary outcome analysis (intention-to-treat): IPC = 1.7% missing, 10.2% dead; No IPC = 1.2% missing, 12.2% dead
1.5% loss to follow-up for 6m outcomes plus 24% who had died by 6 months – no differential attrition rates</td></tr>
<tr><td>Intervention & comparator</td><td>IPC vs No IPC; Thigh-length bilateral IPC delivering sequential pressure; worn 24hrs per day over 30 days (or until mobile or discharged)
Background use of aspirin and some heparin

Background pharmacological treatment was similar prior to and following randomisation, but use of anti-embolism stockings was greater in the IPC group during the treatment phase of the trial:

<table>
<tr><th>Background pharmacological treatment:
- at recruitment</th><th>IPC (n=1438)</th><th>No IPC (n=1438)</th></tr>
<tr><td>On warfarin at recruitment</td><td>25 (2%)</td><td>29 (2%)</td></tr>
<tr><td>On heparin at recruitment</td><td>86 (6%)</td><td>78 (5%)</td></tr>
<tr><td>Taken antiplatelet medication in past 24 hours at recruitment</td><td>970 (67%)</td><td>971 (68%)</td></tr>
<tr><td>Received thrombolysis since admission</td><td>249 (17%)</td><td>255 (18%)</td></tr>
<tr><td colspan="3">- during treatment phase (30 days)</td></tr>
<tr><td>Prophylactic dose anticoagulant prescribed (heparin / LMWH) post-randomisation</td><td>248 (17%)</td><td>240 (17%)</td></tr>
<tr><td>Treatment dose anticoagulant prescribed (heparin / LMWH) post-randomisation</td><td>182 (13%)</td><td>219 (15%)</td></tr>
<tr><td>Elastic anti-embolism stockings (ES) worn</td><td>118 (8%)</td><td>42 (3%)</td></tr>
</table>
</td></tr>
<tr><td>Outcomes</td><td>Primary outcome was any proximal DVT within 30days of randomisation. Secondary outcomes included:
• All cause mortality and survival to final follow up at about six months
• Disability at 6 month (Oxford handicap scale)
• Pulmonary embolism (confirmed by imaging or autopsy) to 6 months
• Symptomatic DVT (proximal only and combined distal or proximal) to six months</td></tr>
</table>

	• Fractures for 30 days • Skin breaks for 30 days • Asymptomatic DVT (proximal only and combined distal or proximal) for 30 days detected by compression duplex ultrasound
Notes	Included ICH but subgroup analysis by stroke pathology for primary outcome Funded by CSO and HTA

Study: CLOTS 3	**Outcome: Mortality/Survival**
Bias	No serious – although patients and healthcare staff not blinded
Indirectness	No serious – although minority of patients had haemorrhagic stroke
Inconsistency	No serious
Imprecision	Serious – not powered to detect survival benefit
Quality of evidence	**Moderate –** a survival analysis demonstrated an effect of IPC (p=0.045) although diff of proportion dead at 6 months did not reach p<0.05.
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious although minority of patients had haemorrhagic stroke
Inconsistency	No serious
Imprecision	Serious – although not powered to detect difference in OHS
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious although minority of patients had haemorrhagic stroke
Inconsistency	No serious
Imprecision	**Serious** because very few events, and low autopsy rate
Quality of evidence	**Moderate**
	Outcome: Symptomatic DVT
Bias	Serious because patient/ healthcare workers unblinded
Indirectness	No serious although minority of patients had haemorrhagic stroke
Inconsistency	No serious
Imprecision	Serious **–** not powered to detect symptomatic DVT
Quality of evidence	**Low**
	Outcome: Fractures
Bias	No serious – objective measure
Indirectness	No serious although minority of patients had haemorrhagic stroke
Inconsistency	Serious – not powered to detect difference
Imprecision	**Moderate**
	Outcome: Skin breaks
Bias	Very Serious – based on casenote review by unblinded person
Indirectness	Serious – little indication of whether breaks associated with IPC
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**Low**

	Outcome: All DVT (including asymptomatic)
Bias	No serious – mostly asymptomatic , based on blinded imaging
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**
Study reference (name)	Prasad (1982)[1]
Methods	Single centre RCT in UK Method of randomisation unclear Blinding not stated
Participants or study population	26 hospitalised stroke patients (excluding coma); within 72 hours of having acute stroke; weakness of up to 2/6 motor power in one or both limbs. Level of mobility mot stated Mean age: 79yrs;
Intervention & comparator	IPC vs No IPC Calf-length IPC delivering circumferential compression; worn bilaterally, continuously for first 24hrs then 3x 3hrs per day over 9 days.
Outcomes	• All cause mortality by day 10- IPC 2/13, Control 0/13 • Any DVT (symptomatic and asymptomatic , proximal and distal combined) measured with radiolabelled fibrinogen only to 10 days–IPC 6/13, Control 6/13. one symptomatic DVT but not stated in which treatment group.
Notes	Type of stroke not reported

Study: Prasad 1982	**Outcome: Mortality/Survival**
Bias	Serious – methods of randomisation not described and no blinding
Indirectness	No serious
Inconsistency	No serious
Imprecision	Very serious – not powered
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	Serious – methods of randomisation not described and no blinding
Indirectness	Serious - Only Isotope scanning for DVT
Inconsistency	**No serious**
Imprecision	Very serious – not powered
Quality of evidence	**Low**

Study reference (name)	**Spinelli 2006**
Methods	Single centre RCT in Italy Method of randomisation unclear Blinding not stated
Participants or study population	100 hospitalised stroke patients ; within 48 hours of having acute stroke; weakness in leg <4/5. ICH excluded by brain imaging

[1] Only mortality data are included in outcome analyses because separate data for symptomatic and asymptomatic DVT are not reported.

	Excluded those with CI to anticoagulation and leg wounds Median age: 80years, Male 35%
Intervention & comparator	IPC plus LMWH vs No IPC plus LMWH Calf-length IPC Venaflow ® (AIRCAST) devices worn bilaterally,
Outcomes	All cause mortality in hospital Symptomatic DVT – but method of confirming DVT unclear
Notes	Results only in abstract and poster

Study: Spinelli 2006	**Outcome: Mortality/Survival**
Bias	Serious – methods of randomisation not described and no blinding. Follow up to discharge only
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to identify an effect for this outcome
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	Serious – methods of randomisation not described and no blinding
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to identify an effect for this outcome
Quality of evidence	**Low**

Anticoagulation (regimes aimed at VTE prophylaxis?)

Included RCTS

Study reference (name)	**Chaudhary 2002**
Methods	Randomisation not described Placebo controlled Exclusions during trial: none Losses to FU: none
Participants or study population	India, 30 participants, Age ~58yrs 100% CT before entry Ischaemic stroke - time not otherwise defined – enrolled within 24 hours. Background treatment with aspirin, steroids, mannitol and glycerol
Intervention & comparator	Rx: parnaparin 0.3 ml sc bid for 10 days versus placebo
Outcomes	Neurological score at 10 days, Death and Barthel Index at 3 months. Significant improvement in neurological score at 10 days with LMWH
Notes	Excluded: CT with ICH, coagulopathy

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious
Inconsistency	No Serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**

Study reference (name)	Duke 1983
Methods	Random number list controlled by pharmacy Doctor, patient, and assessor blind Exclusions during trial: none Losses to FU: none
Participants or study population	Canada – two hospitals 65 participants ? age, ? sex 81% CT before entry 'Partial stable' ischaemic stroke < 48 hours since stroke onset
Intervention & comparator	Rx: heparin 5000 IU sc 8 hourly Control: placebo Duration: 7 days
Outcomes	Death – but not reported in the 65 enrolled in this arm DVT (systematic I-125 scan) Intracranial haemorrhage (symptomatic) – none reported Extracranial haemorrhage – none reported Disability at 3 and 12 months – not reported for 65
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 1 year

	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	Serious - Only Isotope scanning for DVT
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – small numbers
Quality of evidence	**Low**
Study reference (name)	**Elias 1990**
Methods	Sealed envelopes (? opaque and sequentially numbered) Non-blind Exclusions during trial: none Losses to FU: 2 in Rx group
Participants or study population	Europe 30 participants Mean age 68 years 57% male 100% CT before entry Ischaemic stroke with immobility Less than 48 hours since stroke onset
Intervention & comparator	Rx: CY 222 (LMWH) 15,000 anti-Xa units sc 24 hourly Control: no treatment Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic I-125 scan, confirmed on venography) Major extracranial haemorrhage
Notes	Ex: BP > 220/120, coma FU: 14 days

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious

Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Symptomatic DVT
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious – DVT on isotope were confirmed on Duplex
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – very small numbers
Quality of evidence	**Low**

Study reference (name)	**FISS 1995**
Methods	Sequentially numbered boxes containing identical syringes Doctor, patient, and assessor blind Exclusions during trial: 4 in Rx group (survival status known for all except one) Losses to FU: 2 in Rx group
Participants or study population	Hong Kong 312 participants Mean age 67 years 58% male 100% CT before entry Ischaemic stroke with motor deficit Less than 48 hours since stroke onset
Intervention & comparator	Rx: nadroparin (LMWH) sc (randomised between 4100 anti-Xa units 12 hourly versus 24 hourly) Control: placebo Duration: 10 days All surviving participants received aspirin 100 mg/day after 10 days
Outcomes	Death plus cause of death Functional outcome (dependency assessed using International Stroke Trial simple questions) PE (symptomatic) Intracranial haemorrhage (symptomatic and systematic CT) Recurrent stroke Major extracranial haemorrhage Myocardial infarction
Notes	Ex: over 80 years, BP > 180/120 mmHg, previous disabling stroke, bleeding risk, imminent death FU: 6 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for mortality
Quality of evidence	**Moderate**
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious

Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**
	Outcome: Recurrent stroke
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect recurrent stroke
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	Serious – included mobile patients
Inconsistency	No serious
Imprecision	Serious – not powered to detect PE
Quality of evidence	**Low**
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect major bleeding
Quality of evidence	**Moderate**
	Outcome: Minor bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**
Study reference (name)	**FISS BIS**
Methods	Sequentially numbered boxes Doctor, patient and assessor blind Exclusions during trial: unknown Losses to FU: unknown
Participants or study population	International 766 participants Mean age unknown % male unknown 100% CT before entry Ischaemic stroke with motor deficit < 24 hours since stroke onset
Intervention & comparator	Rx: nadroparin (LMWH) 86 units/kg sc once daily versus 86 units/kg sc 12 hourly Control: placebo Duration: 10 days
Outcomes	Death Functional Outcome (Barthel Index score < 85 = dependent) & IST questions Intracerebral haemorrhage (symptomatic CT)
Notes	Not reported in full – only abstract, Ex: mild stroke, coma FU: 6 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious

Inconsistency	No serious
Imprecision	Serious – not powered to determine survival benefit
Quality of evidence	**Moderate**
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**
	Outcome: Recurrent stroke
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to determine effect on recurrent stroke
Quality of evidence	**Moderate**
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to determine effect on recurrent stroke
Quality of evidence	Moderate

Study reference (name)	**IST 1997**
Methods	Telephone randomisation Unblinded; dependency assessment mainly blinded Exclusions during trial: none Losses to FU: data 99.99% complete for 14-day outcome and 99.2% complete for 6-month outcome
Participants or study population	International 19,435 participants 61% > 70 years 54% male 67% CT prior to randomisation, 29% CT after randomisation Ischaemic stroke < 48 hours since stroke onset
Intervention & comparator	Rx: sc heparin (5000 IU or 12,500 IU 12 hourly), aspirin 300 mg, both, or neither (factorial design) Duration: 14 days or until discharge from hospital
Outcomes	Death Functional outcome (validated simple questions) Recurrent stroke PE Intracranial haemorrhage (symptomatic CT) Extracranial haemorrhage
Notes	Ex: small likelihood of worthwhile benefit; high risk of adverse effect (e.g. hypersensitivity of aspirin, recent GI bleed or peptic ulcer disease, already on long-term anticoagulation) FU: 6 months. For purpose of meta-analysis the outcomes in the 5000IUbd with, or without aspirin groups (n=4860) were compared with the avoid any heparin with, or without, aspirin group (n=9718).

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious

Imprecision	No serious
Quality of evidence	**High**
	Outcome: Disability at 6 months
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**
	Outcome: Recurrent stroke
Bias	Serious – based on note review by unblinded person
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	Serious – based on note review by unblinded person
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on PE
Quality of evidence	**Low**
	Outcome: Major bleeding
Bias	Serious – based on note review by unblinded person
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**Moderate**

Study reference (name)	**Kwiecinski 1995**
Methods	Unknown method of randomisation Blinding not stated Exclusions during trial: unknown Losses to FU: unknown
Participants or study population	Poland 120 participants Mean age 57 years 65% male 100% CT before entry Enrolled less than 48 hours after ischaemic stroke
Intervention & comparator	Rx: fraxparin (LMWH) 0.6 ml 12 hourly for one week, then 0.3ml 12 hourly for one week Control: placebo Duration: 14 days
Outcomes	Death Functional outcome Intracerebral haemorrhage (symptomatic CT) Symptomatic DVT and PE during treatment period
Notes	Only published as an abstract; Ex: > 65 years, comatose, severe comorbidity, uncontrolled hypertension FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	Serious
Indirectness	No serious but young and included mobile

Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on survival
Quality of evidence	**Low**
	Outcome: Disability at 6 months
Bias	Serious
Indirectness	No serious but young and included mobile
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on disability
Quality of evidence	**Low**
	Outcome: Recurrent stroke
Bias	Serious
Indirectness	No serious but young and included mobile
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on recurrent stroke
Quality of evidence	**Low**
	Outcome: Pulmonary embolism
Bias	Serious
Indirectness	No serious but young and included mobile
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on PE
Quality of evidence	**Low**
	Outcome: Major bleeding
Bias	Serious
Indirectness	No serious but young and included mobile
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on major bleeds
	Outcome: Symptomatic DVT
Bias	Serious
Indirectness	No serious but young and included mobile
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on survival
Quality of evidence	**Low**

Study reference (name)	McCarthy 1977
Methods	Sealed envelopes (? opaque and sequentially numbered) only DVT assessment blind Exclusions during trial: none Losses to FU: none
Participants or study population	United Kingdom 32 participants Mean age 78 years 34% male No CT, 100% LP before entry Any stroke with no blood in CSF Less than 48 hours since stroke onset
Intervention & comparator	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 14 days
Outcomes	Death but not cause of death DVT (systematic I-125 scan)
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 1 month

Study:	Outcome: Mortality/Survival
Bias	Serious – unclear concealment, open trial
Indirectness	Serious – ICH not excluded,
Inconsistency	Not serious
Imprecision	Serious – very small numbers
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	Serious – unclear concealment, open trial
Indirectness	Serious – ICH not excluded, Isotope scanning only
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	No serious – but only because event rate so high
Quality of evidence	**Low**

Study reference (name)	McCarthy 1986
Methods	Sealed envelopes (? opaque and sequentially numbered) only DVT assessment blind Exclusions during trial: none Losses to FU: none
Participants or study population	United Kingdom 305 participants Mean age 76 years 43% male No CT before entry All strokes (10% haemorrhagic on autopsy) Less than 48 hours since stroke onset
Intervention & comparator	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 14 days Antiplatelet therapy during follow up not reported
Outcomes	Death , Death with PE DVT (only systematic I-125 scan)
Notes	Ex: BP > 120 diastolic, bleeding risk FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	Serious – unclear concealment, open trial
Indirectness	Serious – ICH not excluded, Isotope scanning only
Inconsistency	Not Serious
Imprecision	Serious – not powered to detect effect on all cause mortality
Quality of evidence	**Low**
Study:	**Outcome: Death with PE**
Bias	Serious – unclear concealment, open trial
Indirectness	Serious – ICH not excluded,
Inconsistency	Not Serious
Imprecision	Serious – not powered to detect effect on death with PE
Quality of evidence	**Low**
	Outcome: All DVT (including asymptomatic)
Bias	Serious – unclear concealment, open trial
Indirectness	Serious – ICH not excluded, Isotope scanning only
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	No serious – but only because event rate so high
Quality of evidence	**Low**
Study reference (name)	**Pince 1981**
Methods	Sealed envelopes (? opaque and sequentially numbered) Non-blind Exclusions during trial: Rx 0, control 4 participants (2 with intracranial haemorrhage) Losses to FU: none
Participants or study population	France 80 participants 30 to 92 years 62% male No CT, 100% LP before entry Ischaemic stroke affecting the leg Less than 7 days since stroke onset (89% < 48 hours)
Intervention & comparator	Rx: heparin 5000 IU sc 8 hourly Control: no treatment Duration: 10 days
Outcomes	Death but not cause of death DVT (systematic I-125 scan) PE Major extracranial haemorrhage – none reported
Notes	Ex: bleeding risk FU: 10 days

Study:	**Outcome: Mortality/Survival**
Bias	Serious
Indirectness	Serious – ICH not excluded by imaging
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Low
	Outcome: Pulmonary embolism
Bias	Serious
Indirectness	Serious – ICH not excluded by imaging
Inconsistency	No serious
Imprecision	Serious – very small numbers

Quality of evidence	Low
	Outcome: Symptomatic DVT
Bias	Serious
Indirectness	Serious – ICH not excluded by imaging
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – very small numbers
Quality of evidence	Low
	Outcome: All DVT (including asymptomatic)
Bias	Serious
Indirectness	Serious – ICH not excluded by imaging
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Low
Study reference (name)	**Prins 1989**
Methods	Sequentially numbered identical syringes Double-blind Exclusions during trial: none Losses to FU: none
Participants or study population	Netherlands 60 participants 78% > 70 years 52% male 100% CT before entry Ischaemic stroke less than 72 hours since stroke onset
Intervention & comparator	Rx: dalteparin (LMWH, Kabi 2165) 2500 anti-Xa units sc 12 hourly Control: placebo Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic I-125 scan confirmed with venography but not clear whether all cases) PE Intracranial haemorrhage (symptomatic plus systematic CT) Major extracranial haemorrhage
Notes	Ex: coma FU: 14 days

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Intracranial bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious

Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious – but unclear if all DVT confirmed on Venography
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – very small numbers
Quality of evidence	**Low**
Study reference (name)	**Sandset 1990**
Methods	Sequentially numbered identical ampoules Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: none
Participants or study population	Norway 103 participants 47 to 90 years 45% male 100% CT before entry Non-cardioembolic ischaemic stroke Less than 72 hours since stroke onset
Intervention & comparator	Rx: dalteparin (LMWH, Kabi 2165) 3000 to 5500 anti-Xa U sc 24 hourly Control: placebo Duration: 14 days
Outcomes	Death plus cause of death DVT (systematic venography or B mode ultrasound) PE (symptomatic plus autopsy in 5/6 deaths) – non fatal Pes not confirmed by imaging Intracranial haemorrhage (systematic CT) Major extracranial haemorrhage
Notes	Ex: BP > 120 diastolic, coma, bleeding risk FU: 28 days

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Moderate
	Outcome: Intracerebral bleed
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Moderate
	Outcome: Pulmonary embolism
Bias	No serious

Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Moderate
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Moderate
	Outcome: Symptomatic DVT
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	Moderate
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – very small numbers
Quality of evidence	Low
Study reference (name)	**Turpie 1987**
Methods	Sequentially numbered identical containers Double-blind Exclusions during trial: none Losses to FU: none
Participants or study population	Canada 75 participants 28 to 90 years 53% male 100% CT before entry Non-cardioembolic ischaemic stroke with immobility Less than 7 days since stroke onset
Intervention & comparator	Rx: danaparoid (heparinoid Org 10172) 750 anti-Xa units sc 12 hourly Control: placebo Duration: 14 days or prior discharge Antiplatelet therapy during follow up not reported
Outcomes	Death plus cause of death DVT (systematic I-125 scan + plethysmography with venography) PE (symptomatic) Intracranial haemorrhage (symptomatic CT) Extracranial haemorrhage Recurrent stroke
Notes	Ex: bleeding risk FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious - very small numbers

Quality of evidence	**Moderate**
	Outcome: Recurrent stroke
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious - very small numbers
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious - very small numbers
Quality of evidence	
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious - very small numbers
	Outcome: Minor bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious - very small numbers
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious - very small numbers
Quality of evidence	**Low**
Study reference (name)	**Vissinger 1995**
Methods	Coded containers administered sequentially to enrolled participants Doctor, patient and assessor blind Exclusions during trial: none Losses to FU: 31/50 participants lost to 6-month follow up
Participants or study population	Denmark 50 participants Mean age 71.8 years 58% male 66% CT before entry - haemorrhage excluded in remainder by cerebral scintigraphy Non-embolic ischaemic stroke with motor deficit < 24 hours since stroke onset
Intervention & comparator	Rx: tinzaparin (LMWH) 3500 anti-Xa IU sc once daily Control: placebo Duration: 14 days or until full mobilisation
Outcomes	Death DVT (venography) PE (symptomatic)
Notes	Exclusion criteria: < 50 years old, hypertension (BP > 200/120 mmHg), coma, aphasia, bleeding risk, oral anticoagulant

	treatment, severe hepatic or renal disease, clinical suspicion of DVT or PE FU: 12 to 14 days and 6 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers of patients
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers of patients
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – very small numbers of patients
Quality of evidence	**Low**

Included RCTs of UFH vs LMWH or Heparinoids

Study reference (name)	**Dumas 1994**
Methods	Sealed envelope - Sequentially numbered identical containers Double blind Intention to treat No loss to FU
Participants or study population	Europe 76 male, 103 female, mean age 72 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke onset
Intervention & comparator	Rx: Org 10172 sc (1250 anti-Xa units 24-hourly) Control: heparin sc (5,000 IU 12-hourly) Duration: 9 to 13 days No background use of antiplatelet allowed
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP greater than 200/120, bleeding risk FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on Death

Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on stroke
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on PE
Quality of evidence	**Moderate**
	Outcome: Extracranial bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect effect on major bleeding
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	No serious
Quality of evidence	**Moderate**

Study reference (name)	**Hageluken 1992**
Methods	Sequentially numbered containers Single blind (assessor) Intention to treat No loss to FU
Participants or study population	Europe 79 male, 66 female, mean age 69 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke onset
Intervention & comparator	Rx: Org 10172 sc (375 anti-Xa units 24-hourly); Org 10172 sc (750 anti-Xa units 24-hourly); Org 10172 sc (1250 anti-Xa units 24-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 9 to 11 days
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP greater than 200/120, bleeding risk FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome

Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Low**

Study reference (name)	**Hillbom 1994**
Methods	Sequentially numbered containers Double blind Intention to treat No loss to FU
Participants or study population	Finland 127 male, 85 female, mean age 69 years 100% CT before entry Ischaemic stroke with leg paresis for more than 24 hours since stroke onset
Intervention & comparator	Rx: enoxaparin (40 mg once daily) Control: heparin sc (5000 IU 8-hourly) Duration: 10 ± 2 days or discharge if sooner
Outcomes	Death DVT (systematic venography) PE (symptomatic) Extracranial haemorrhage Intracranial haemorrhage (systematic CT)
Notes	EX: specified by protocol - includes bleeding risk; Glasgow Coma Scale less than 9; pre-existing DVT FU: 3 months Sponsoring pharmaceutical company stopped before planned sample size of 400 patients recruited, because of very slow recruitment rate

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious

Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Extracranial bleeding
	No serious
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – not powered for this outcome
Imprecision	**Moderate**
	Outcome: Symptomatic DVT
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	Serious – significant heterogeneity between trials
Imprecision	Serious – not powered for this outcome
Quality of evidence	**Low**

Study reference (name)	**Prevail 2007**
Methods	Blocked and stratified randomisation, telephone to central randomisation system Study treatment was not blinded Intention to treat Losses to follow up: 32 (15 Rx, 17 control)
Participants or study population	International 994 male, 768 female, mean age 66 years 100% CT or MRI before entry Ischaemic stroke and unable to walk unassisted Less than 48 hours since stroke onset NIHSS score 2 or more
Intervention & comparator	Rx: enoxaparin 40 mg sc once daily Control: heparin sc (5000 IU 12-hourly) Duration: 10 days (range 6 to 14)
Outcomes	Death DVT (systematic venography or ultrasound if venography not possible) PE (symptomatic) Extracranial haemorrhage

	Intracranial haemorrhage (systematic CT) Modified Rankin Scale
Notes	Ex: specified by protocol FU: 90 days Sponsored by Sanofi-Aventis (Paris, France)

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Disability
Bias	Serious – no blinded assessment
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
Quality of evidence	**Low**
	Outcome: Intracranial haemorrhage
Bias	No serious – not blinded but confirmed by blinded committee
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious– not blinded but confirmed by blinded committee
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: Extracranial bleeding
Bias	No serious– not blinded but confirmed by blinded committee
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
	Moderate
	Outcome: Symptomatic DVT
Bias	No serious– not blinded but confirmed by blinded committee
Indirectness	No serious
Inconsistency	No serious
Imprecision	Not powered for this outcome
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	No serious
Quality of evidence	**High**

Study reference (name)	**Protect 2006**
Methods	R = computer-generated randomisation list Double-blind Intention to treat Losses to follow up: 67 (34 Rx, 33 control)

Participants or study population	European Union 313 male, 232 female, 18 to 85 years, mean age 67 years 100% CT before entry Ischaemic stroke with leg paresis Less than 24 hours since stroke onset NIHSS score 4 to 30
Intervention & comparator	Rx: certoparin sc (3000 U once daily) plus 2 injections of placebo Control: heparin sc (5000 IU 8-hourly) Duration: 12 to 16 days
Outcomes	Death Proximal leg DVT (ultrasound) PE (symptomatic) – none occurred Extracranial haemorrhage Intracranial haemorrhage (systematic CT)
Notes	Ex: specified by protocol - includes bleeding risk, body weight less than 55 kg FU: 3 months Sponsored by Novartis (Nürnberg, Germany)

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
	Moderate
	Outcome: Extracranial bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**

Study reference (name)	**Stiekema 1988 (Hossman et al 1986)**
Methods	Sequentially numbered containers Single blind (assessor) Not quite intention to treat because 2 patients excluded from analysis
Participants or study population	Europe 43 male, 39 female, 21 to 91 years 100% CT before entry Ischaemic stroke with leg paresis Less than 72 hours since stroke

Intervention & comparator	Rx: loading dose 1000 anti-Xa units iv, then Org 10172 sc (1250 anti-Xa units 12-hourly) or Org 10172 sc (750 anti-Xa units 12-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 10 days
Outcomes	Death + cause of death DVT (systematic I^{125} scan with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT) Extracranial haemorrhage
Notes	Ex: BP greater than 200/120, bleeding risk FU: 14 days

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
	Moderate
	Outcome: Extracranial bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – not powered to detect difference in this outcome
Quality of evidence	**Moderate**

Study reference (name)	**Turpie 1992**
Methods	Sequentially numbered identical containers Double blind Intention to treat No loss to FU
Participants or study population	Canada 38 male, 49 female, mean age 72 years 100% CT before entry Non-embolic ischaemic stroke with leg paresis

	Less than 7 days since stroke onset
Intervention & comparator	Rx: Org 10172 sc (750 anti-Xa units 12-hourly) Control: heparin sc (5000 IU 12-hourly) Duration: 14 days
Outcomes	Death DVT (systematic I^{125} scan + plethysmography with venography) PE (symptomatic) Intracranial haemorrhage (systematic CT)
Notes	Ex: bleeding risk; pre-existing DVT FU: 3 months

Study:	**Outcome: Mortality/Survival**
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Intracranial haemorrhage
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Pulmonary embolism
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**
	Outcome: Major bleeding
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
	Moderate
	Outcome: All DVT (including asymptomatic)
Bias	No serious
Indirectness	No serious
Inconsistency	No serious
Imprecision	Serious – very small numbers
Quality of evidence	**Moderate**