National Institute for Health and Care Excellence

Final

Addendum to Clinical Guideline 144, Venous thromboembolic diseases in adults: diagnosis, management and thrombophilia testing

Clinical Guideline Addendum 144.1

Evidence reviews on thrombolysis for pulmonary embolism and compression stockings to prevent post-thrombotic syndrome

Methods, evidence and recommendations

The evidence reviews in this addendum underpin the 2015 recommendations in the NICE guideline

Final

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on venous thromboembolic diseases: the management of thromboembolic diseases and the role of thrombophilia testing (NICE guideline CG144) was reviewed in 2014 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence that supported the need for an update of the sections of the guideline in relation to two areas: thrombolysis in those with confirmed pulmonary embolism and haemodynamic stability with right ventricular dysfunction, and stockings to prevent post-thrombotic syndrome in those with proximal deep vein thrombosis. The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), taking into account comorbidities, contraindications and drug costs, with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism).

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer. [2012]

1.2.7 Consider pharmacological systemic thrombolytic therapy for patients with pulmonary embolism (PE) and haemodynamic instability (see also recommendation 1.2.1 on pharmacological interventions for deep vein thrombosis [DVT] and PE). [2012]

1. **Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability with or without right ventricular dysfunction (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). If patients develop haemodynamic instability, see recommendation 1.2.7 [new 2015]**

2. **Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or for the prevention of venous thromboembolic disease recurrence after a proximal deep vein thrombosis (DVT). This recommendation does not cover the use of elastic stockings for the management of leg symptoms after DVT [new 2015].**

1.3 Patient-centred care

This guideline offers best practice advice on the care of adults with venous thromboembolic diseases.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In

Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

The scoping phase of this update (including development of the review protocols, see Appendix C:) was based on the process and methods described in the guidelines manual 2012. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for the updates pilot programme (2013). The development and validation phases of this update followed the new guidelines manual 2014. For details specific to the evidence reviews, see Sections 2.1.2 and 2.2.2.

2 Evidence review and recommendations

Introduction

Venous thromboembolic (VTE) diseases include deep vein thrombosis (DVT), pulmonary embolism (PE) and the long-term complications that can arise from these conditions.

A DVT is a blood clot (thrombus) that forms in a deep vein, most commonly in the calf muscle or, less often, in the thigh, arms or elsewhere in the body. Acute PE can be life-threatening. It is caused when part or all of a thrombus breaks free and travels in the bloodstream (embolises) to obstruct arteries in the lung. Critical factors affecting prognosis in PE include the haemodynamic impact and whether or not the right ventricle of the heart has sustained injury or been functionally compromised due to the obstructive effects of the embolus on circulatory blood flow.

Current standard treatment for venous thromboembolic disease is anticoagulation to prevent further clotting. Anticoagulants carry a bleeding risk. There is wide variation in practice, but patients are usually given an initial brief course of heparin treatment which overlaps into a 3–6 month course of a vitamin K antagonist (VKA) such as warfarin. Patients on warfarin require regular monitoring during treatment. The newer oral anticoagulants (NOACs) are increasingly being used and do not normally require monitoring.

There is also the potential to dissolve clots using thrombolysis. Thrombolytic therapy acts more quickly than anticoagulation, and may reduce the risk of fatal PE and of developing chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a long-term complication of non-fatal PE whereby clots that are not reabsorbed into the bloodstream increase resistance to blood flow through the lung, causing shortness of breath and decreased exercise tolerance, resulting in pulmonary hypertension and progressive right heart failure.

Thrombolytics can, however, increase the risk of major bleeding, including intracerebral haemorrhage. NICE CG144 currently only recommends systemic thrombolysis as a possible treatment option in patients with acute PE who are haemodynamically unstable and so considered at high risk of early mortality (18-65% mortality within 30 days; Belohlavek et al. 2013).

The recent surveillance review of CG144 found new evidence relating to the use of systemic thrombolysis in a subgroup of patients with acute PE who are considered to be at ‘intermediate risk’ of early mortality (3-15% within 30 days). These patients are haemodynamically stable (normotensive) on presentation, but have evidence of right ventricular (RV) dysfunction or injury (Belohlavek et al. 2013). This new evidence may impact on the current guideline regarding thrombolytic therapy for PE.

Post thrombotic syndrome (PTS) is a chronic condition that develops in 20-50% of people who experience a non-fatal DVT of the lower limb. It usually occurs within 2 years of an acute episode of DVT and is characterised by symptoms that can range from minor skin changes and itching, varicose veins, aching pain and leg swelling to chronic leg ulceration. External compression is used in patients with acute DVT with the aim of preventing PTS. CG144 currently recommends daily use (for at least 2 years) of knee-length graduated compression stockings (with an ankle pressure >23mmHg) worn on the affected leg following confirmed proximal DVT. The surveillance review also found new evidence that may impact on this section of the guideline.

2.1 Review question 1: Thrombolysis for pulmonary embolism

2.1.1 Review question

What is the effectiveness of thrombolysis given in addition to standard accepted anticoagulation therapy compared with anticoagulation therapy alone in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?

2.1.2 Clinical evidence review

A systematic search was conducted (see Appendix D.1.1) which identified 2528 articles. The titles and abstracts were screened and 70 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C.1). Of these, 63 were excluded as they did not meet the criteria and 7 studies met the criteria and were included. A summary of the included studies is presented in Table 1.

A review flowchart is provided in Appendix E.1.1, and the excluded studies (with reasons for exclusion) are shown in Appendix F.1.1.

Methods

Outcomes were chosen and prioritised by the topic experts, and reviewed by core Committee members before the review was undertaken. All-cause mortality and major bleeding were chosen as critical outcomes for decision making. During discussion of outcomes, the topic experts noted it was unlikely that studies would be sufficiently powered to detect a difference in all-cause mortality. Nevertheless, it was agreed this was a critical outcome. In consideration of this issue, the topic experts proposed inclusion of an additional composite clinical outcome of 'death or haemodynamic collapse / treatment escalation'. The following outcomes were also considered important for decision-making: VTE-related mortality, VTE recurrence, quality of life, chronic thromboembolic pulmonary hypertension (CTEPH), length of hospital stay.

Only one study reported length of hospital stay (Sharifi 2013). This open-label study differed from other included studies in that a lower dose of thrombolysis was used; it also included patients who may not meet the review protocol criteria for evidence of RV dysfunction. The length of stay data are presented in the evidence table (see Appendix G.1.1) but were not extracted for analysis due to concerns about generalisability.

Where more than one study assessed a specified outcome, the data were combined using a pair-wise meta-analysis. The Mantel-Haenszel method was used for the dichotomous outcomes included in the meta-analyses. A random effects model was chosen because treatment effects were unlikely to be identical across studies due to differences in inclusion criteria and in the types and doses of thrombolytic and anticoagulant used. The I^2, chi^2 and tau^2 statistics were calculated to assess heterogeneity (a tau^2>1.0 was considered to indicate significant statistical heterogeneity). Forest plots from these meta-analyses are in Appendix I.1.

The quality of evidence for each outcome (where evidence was available) was considered using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group. For full evidence tables and GRADE profiles see Appendices G.1.1 and H.1.

All 7 included studies were randomised controlled trials. Typical reasons for downgrading evidence for risk of bias included selection bias (baseline differences in treatment groups, or where data were analysed only for a subgroup of study participants that met the review

protocol inclusion criteria for this update). Lack of blinding (of clinicians or outcome assessors), including open label trials, also led to downgrading evidence for risk of bias.

The protocols of three included studies (Konstantinides 2002, Kline 2014, Meyer 2014) permitted clinician unblinding in the event of patients requiring emergency treatment, which could include secondary 'rescue' thrombolytic therapy. The proportion of patients in whom treatment allocation was revealed in order to make emergency treatment decisions ranged from 2.6% (Meyer 2014) to 16% (Konstantinides 2002), with significant differences between treatment groups in the indications and proportions of patients subsequently given secondary thrombolysis. A subgroup analysis was therefore undertaken for each outcome to compare studies that did permit per-protocol unblinding with those that did not (see forest plots in Appendix I.1). The presence of a subgroup effect was assessed by examining the statistical significance of a test for subgroup differences. A p-value of less than 0.05 was taken as evidence for a possible subgroup effect. As no such evidence was found, the GRADE profiles in Appendix H.1 (Table 15) present data for all studies combined that assessed each specified outcome.

Inconsistency was assessed where data were combined in a meta-analysis. The degree of heterogeneity and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group. In two instances relating to major bleeding outcomes serious inconsistency was identified. A sensitivity analysis showed results were significantly influenced by one study (Konstantinides 2002) in which a relatively high proportion of control group patients (23%) received secondary thrombolysis due to worsening symptoms. The GRADE profiles for these bleeding outcomes report results from the sensitivity analysis, after this study was excluded.

Indirectness was assessed by noting whether the evidence directly applied to the parameters specified in the review protocol. In two studies, not all participants met the review protocol inclusion criteria for confirmed RV dysfunction. No studies reported data for CTEPH, a long-term complication of non-fatal PE, but two studies reported outcomes that may predict development of the condition.

Imprecision of evidence was assessed by determining whether 95% confidence intervals for effect estimates crossed thresholds for clinically important benefit or harm. A routine search of the Core Outcome Measures in Effectiveness Trials (COMET Initiative) database did not yield information on accepted minimum clinically important difference thresholds (MIDs) for any of the outcomes under consideration in this review and no published MIDs were found in a search of the medical literature. In the previous guideline, GRADE default MIDs had been adopted (RR=0.75 and 1.25 for dichotomous outcomes). Following discussion with the topic experts it was agreed that the GRADE default MIDs would also be used for this update. If thresholds for clinical benefit, no effect and clinical harm were all incorporated in the 95%CI, imprecision of the evidence was considered to be very serious and downgraded two levels. If the 95%CI incorporated one of the MID thresholds, imprecision was considered serious and the evidence downgraded one level.

Other factors such as publication bias were also considered, but no studies gave rise to serious uncertainty.

Subgroup analyses were conducted for type of thrombolytic agent and patient age group, as specified in the review protocol. A planned subgroup analysis comparing standard and lower-dose thrombolysis was not undertaken because only one small open-label study had used a lower dose (Sharifi 2013). Also, because all included studies used systemic thrombolysis, a planned comparison with catheter-directed administration was not possible. Data were not available to compare outcomes across studies for patients under and over 75 years of age. However, a subgroup analysis was undertaken comparing studies where the mean age of participants was less than 65 years with those in which patients had a mean age ≥65 years, although the results of any subgroup analyses based on means across study samples should always be treated with caution (see Table 16 in Appendix H.1). The largest of the included

studies (Meyer 2014) reported a pre-specified subgroup analysis comparing patients ≤75yrs and >75yrs, the results of which are presented to inform decision-making (see Table 17 in Appendix H.1).

Table 1: Summary of included studies for Review Question 1: Thrombolysis compared with standard anticoagulation for patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction

Study reference (including study design)	Study population	Intervention & comparator	Reported outcomes relevant to review protocol	Comments
Goldhaber et al. (1993) Open-label RCT	n=101 patients ≥18yrs, with symptom onset ≤ 14 days, confirmed diagnosis of PE, systolic BP <200mm. Mean age: 59yrs. 44% male.	Alteplase + unfractionated heparin (UFH) vs UFH only Alteplase administered as 100mg IV infusion over 2 hrs (50mg/hr) prior to UFH	• All-cause mortality (within 14 days or in-hospital, if longer) • Death due to PE (within 14 days or in-hospital, if longer) • Non-fatal recurrence of PE (within 14 days or in-hospital, if longer)	Setting: USA, multicentre (number of participating centres not reported) Open label trial Outcome data have been extracted for a subsample of n=46 patients (46%) with RVD confirmed by echocardiograph at baseline
Konstantinides et al. (2002) Double-blind RCT ('MSPPE3' trial)	n=256 patients, 18-80yrs, symptom onset ≤ 4 days, confirmed diagnosis of PE, normal systolic BP (>90mm Hg) and RVD confirmed by echocardiograph OR confirmed pulmonary hypertension based on right heart catheter study. Mean age: 62yrs. 48% male.	Alteplase + unfractionated heparin (UFH) vs Placebo + UFH Alteplase administered as 10mg bolus followed by 90mg IV infusion over 2 hrs concurrent with UFH	• All-cause mortality (in-hospital or within 30 days, whichever first) • Major bleeding (in-hospital or within 30 days, whichever first) • Composite of all-cause mortality OR clinical deterioration requiring treatment escalation (in-hospital or within 30 days, whichever first) • Death due to PE (in-hospital or within 30 days, whichever first) • Non-fatal recurrence of PE (in-hospital or within 30 days, whichever first)	Setting: Germany (49 medical centres) Protocol permitted unblinding in event of emergency requiring additional therapy (occurred in 41 (16%) cases); significantly more control patients received secondary thrombolysis compared with the intervention group (23.2% vs 7.6%) Majority of patients (approximately 70%) do not meet review protocol inclusion criteria for RVD Study terminated early (intended to recruit 217 to each group) – interim analyses after recruiting 250 patients showed significant difference between

Study reference (including study design)	Study population	Intervention & comparator	Reported outcomes relevant to review protocol	Comments
				groups on primary (composite) outcome
Becattini et al. (2010) Double-blind RCT ('TIPES' trial)	n=58 patients 18-85yrs, with symptom onset ≤ 10 days, confirmed diagnosis of PE, normal systolic BP (≥100 mm Hg) and RVD confirmed by echocardiography within 24 hours of PE diagnosis. Mean age: 68yrs. 40% male.	Tenecteplase + unfractionated heparin (UFH) vs Placebo + UFH Tenecteplase 30-50mg (weight-adjusted dose) administered as IV bolus concurrently with UFH	• All-cause mortality (within 30 days) • Major bleeding (within 7 days) • Clinical deterioration requiring treatment escalation (within 7 days) • Death due to PE (within 30 days) • Non-fatal recurrence of PE (within 30 days)	Setting: Italy (15 medical centres) Study terminated early (intended to recruit 180 patients) Intervention group significantly older (72.1yrs vs 64.5yrs) and had lower heart rate profile (90.3 vs 102.0) than placebo group
Fasullo et al. (2011) Double-blind RCT	n=72 patients 18-75yrs, with symptom onset ≤ 6 hours, confirmed diagnosis of PE, normal systolic BP (>100 mm Hg) and RVD confirmed by echocardiograph. Mean age: 56yrs. 57% male.	Alteplase + unfractionated heparin (UFH) vs Placebo + UFH Alteplase administered as 10mg bolus followed by 90mg IV infusion over 2 hrs concurrent with UFH	• All-cause mortality (within 10 days; within 6 months) • Major bleeding (within 10 days; within 6 months) • Death due to PE (within 10 days; within 6 months) • Non-fatal recurrence of PE (within 6 months) • DVT persistence (within 6 months)	Setting: Italy (3 medical centres)

Study reference (including study design)	Study population	Intervention & comparator	Reported outcomes relevant to review protocol	Comments
Sharifi et al. (2013) Open-label RCT ('MOPETT' trial)	n= 121 adult patients, with PE onset of symptoms ≤10days, plus evidence of thrombus obstruction of ≥2 lobar or main pulmonary arteries, BP >95 and <200/100 mm Hg Mean age: 58yrs. 45% male.	'Low dose' alteplase + low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) vs LMWH/UFH only Alteplase (≤50% of 'standard' dose): 10mg IV bolus followed by 40mg infusion over 2 hours, concurrent with heparin. Approximately 80% in each group received LMWH, 20% UFH.	• All-cause mortality (in-hospital) • Bleeding (not defined; in-hospital) • Non-fatal recurrence of PE (in-hospital) • Pulmonary hypertension (within 28±5 months)	Setting: USA (one medical centre) Not all participants may meet review protocol inclusion criteria for RVD
Meyer et al. (2014) Double-blind RCT ('PEITHO' trial)	n=1005, ≥18years with confirmed acute PE, onset of symptoms ≤15 days, objective evidence of RVD / myocardial injury, systolic BP <180 mm Hg and/or diastolic <110 mm Hg Mean age: 66yrs. 47% male.	Tenecteplase + unfractionated heparin (UFH) vs Placebo + UFH Tenecteplase 30-50mg (weight-adjusted dose) administered as IV bolus concurrently with UFH	• All-cause mortality (within 7 days; within 30 days) • Major bleeding (within 7 days) • Composite of death from any cause or haemodynamic decompensation/ collapse (within 7days) • Death due to PE (within 7 days; within 30 days) • Non-fatal recurrence of PE (within 7 days)	Setting: 13 countries (76 sites) across Europe and North America Intervention group differed at baseline from placebo group on heart rate (94.5bpm vs 92.3bpm) and proportion given LMWH / fondaparinux prior to randomisation (34% vs 27%) Protocol permitted unblinding in event of emergency. Open-label secondary thrombolysis was given to 27 patients (2.6%) - significantly more in the control group compared with the intervention group (4.6% vs 0.8%)

Study reference (including study design)	Study population	Intervention & comparator	Reported outcomes relevant to review protocol	Comments
Kline et al. (2014) Double-blind RCT ('TOPCOAT' trial)	n=83 patients, >17yrs, with confirmed PE diagnosis via CT pulmonary angiography in past 24hrs, normal systolic BP ≥90mm Hg and RVD evidence from echocardiography / elevated Troponin I or T / elevated brain natriuretic peptide (BNP) Mean age: 55yrs; 59% male.	Tenecteplase + low-molecular dose heparin (LMWH) vs Placebo + LMWH Tenecteplase 30-50mg (weight-adjusted dose) administered as IV bolus prior to start of LMWH therapy.	• All-cause mortality (within 5 days) • Death due to PE (within 5 days) • Major bleeding (within 5 days) • Clinical deterioration (shock / intubation; within 5 days) • Non-fatal recurrence of PE (at 3 months) • Quality of Life (at 3 months) • Poor functional capacity (at 3 months)	Setting: USA (8 medical centres) Protocol permitted unblinding in event of emergency requiring additional therapy (occurred in 5 cases (6%) due to serious adverse outcome); no details provided of additional treatment given Study terminated early due to administrative issues - intended to recruit 82 patients to each group

2.1.3 Health economic evidence review

2.1.3.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review question. The evidence was identified by conducting a broad search in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 7 April 2015. The health economic search strategy is detailed in Appendix D.2.2.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *The guidelines manual 2014*.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence. Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (Appendix F.1.2). A flowchart summarising the number of studies included and excluded at each stage of the systematic review can be found in Appendix E.1.2.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H of The guidelines manual 2014*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not required, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted. They may have been revised subsequently by the time of publication.

2.1.3.2 Results of the economic literature review

495 articles were retrieved by the database search. 493 of these were excluded based on title and abstract. 2 full papers were subsequently examined and excluded. Therefore, no economic studies were included in the systematic review.

2.1.3.3 Unit Costs

Table 2 provides the unit costs of anticoagulation and thrombolysis. The Drug Tariff was used to obtain costs unless the medicine did not appear there in which case the BNF was used.

Table 2: Unit costs of anticoagulation and thrombolysis medicines

Medicine	Details	Cost (£)	Source
Anticoagulation			
Dalteparin sodium (Fragmin) (single-dose syringe)	12 500 units/mL, 2500-unit (0.2-mL) syringe	1.86	BNF accessed 12 June 2015
	25 000 units/mL, 5000-unit (0.2-mL) syringe	2.82	BNF accessed 12 June 2015
	25 000 units/mL, 7500-unit (0.3-mL) syringe	4.23	BNF accessed 12 June 2015
	25 000 units/mL, 10 000-unit (0.4-mL) syringe	5.65	BNF accessed 12 June 2015
	25 000 units/mL, 12 500-unit (0.5-mL) syringe	7.06	BNF accessed 12 June 2015
	25 000 units/mL, 15 000-unit (0.6-mL) syringe	8.47	BNF accessed 12 June 2015
	25 000 units/mL, 18 000-unit (0.72-mL) syringe	10.16	BNF accessed 12 June 2015
Dalteparin sodium (amp or vial)	2500 units/mL (for subcutaneous or intravenous use), 4-mL (10 000-unit) amp	5.12	BNF accessed 12 June 2015
	10 000-units/mL (for subcutaneous or intravenous use), 1-mL (10 000-unit) amp	5.12	BNF accessed 12 June 2015
	25 000 units/mL (for subcutaneous use only), 4-mL (100 000-unit) vial	48.66	BNF accessed 12 June 2015
Enoxaparin sodium (Clexane) (pre-filled syringes)	20mg/0.2ml solution for injection	2.27	Drug Tariff April 2015
	40mg/0.4ml solution for injection	3.03	Drug Tariff April 2015

Medicine	Details	Cost (£)	Source
	60mg/0.6ml solution for injection	4.57	Drug Tariff April 2015
	80mg/0.8ml solution for injection	6.49	Drug Tariff April 2015
	100mg/1ml solution for injection	8.03	Drug Tariff April 2015
	120mg/0.8ml solution for injection	9.77	Drug Tariff April 2015
	150mg/1ml solution for injection	11.10	Drug Tariff April 2015
Tinzaparin sodium (Innohep) (syringe)	20 000 units/mL, 0.4-mL (8 000-unit) syringe	4.76	BNF accessed 12 June 2015
	20 000 units/mL, 0.5-mL (10 000-unit) syringe	5.95	BNF accessed 12 June 2015
	20 000 units/mL, 0.6-mL (12 000-unit) syringe	7.14	BNF accessed 12 June 2015
	20 000 units/mL, 0.7-mL (14 000-unit) syringe	8.34	BNF accessed 12 June 2015
	20 000 units/mL, 0.8-mL (16 000-unit) syringe	9.52	BNF accessed 12 June 2015
	20 000 units/mL, 0.9-mL (18 000-unit) syringe	10.71	BNF accessed 12 June 2015
	20 000 units/mL, 2-mL (40 000-unit) vial	34.20	BNF accessed 12 June 2015
Heparin sodium (1000 unit/mL)	1-mL amp	1.49	BNF accessed 12 June 2015
	5-mL amp	3.75	BNF accessed 12 June 2015
	5-mL vial	1.53	BNF accessed 12 June 2015
	10-mL amp	6.46	BNF accessed 12 June 2015
	20-mL amp	4.75	BNF accessed 12 June 2015
Heparin sodium (5000 units/mL)	1-mL amp	2.90	BNF accessed 12 June 2015
	5-mL amp	7.58	BNF accessed 12 June 2015
	5-mL vial	6.31	BNF accessed 12 June 2015
Heparin sodium (25000 units/mL)	0.2-mL amp	3.74	BNF accessed 12 June 2015
	1-mL amp	7.70	BNF accessed 12 June 2015
	5-mL vial	11.11	BNF accessed 12 June 2015
Fondaparinux sodium (Arixtra)	5 mg/mL, 0.3-mL (1.5-mg) prefilled syringe	6.28	BNF accessed 15 June 2015
	5 mg/mL, 0.5-mL (2.5-mg) prefilled syringe	6.28	BNF accessed 15 June 2015
	12.5 mg/mL, 0.4-mL (5-mg) prefilled syringe	11.65	BNF accessed 15 June 2015

Medicine	Details	Cost (£)	Source
	12.5 mg/mL, 0.6-mL (7.5-mg) prefilled syringe	11.65	BNF accessed 15 June 2015
	12.5 mg/mL, 0.8-mL (10-mg) prefilled syringe	11.65	BNF accessed 15 June 2015
Thrombolysis			
Alteplase (Actilyse) (powder for reconstitution)	10 mg (5.8 million units)/vial, per vial (with diluent)	144.00	BNF accessed 12 June 2015
	20 mg (11.6 million units)/vial (with diluent and transfer device)	216.00	BNF accessed 12 June 2015
	50 mg (29 million units)/vial (with diluent and transfer device)	360.00	BNF accessed 12 June 2015
Tenecteplase (Metalyse) (powder for reconstitution)	40-mg (8000-unit) vial with prefilled syringe of water for injection	502.25	BNF accessed 12 June 2015
	50-mg (10 000-unit) vial with prefilled syringe of water for injection	502.25	BNF accessed 12 June 2015

2.1.4 Evidence statements

2.1.4.1 Clinical evidence statements

The GRADE profile (Appendix H.1 Table 15) shows the event rate and relative risk (with 95%CIs) for each outcome. However, because some important outcomes have very low rates of occurrence, for ease of interpretation the evidence is summarised below in terms of absolute risk per 1000 (or per 10,000) thrombolysis-treated patients, compared with the mean event rate per 1000 (or 10,000) patients treated with heparin alone. Figures are derived from the comparator and absolute effect estimate data shown in Table 15.

In patients with acute pulmonary embolism, haemodynamic stability and right ventricular dysfunction:

- Very low quality evidence from 7 trials with 1,641 patients showed it was uncertain if there was a difference in all-cause mortality (within 30 days) in patients treated with adjunctive thrombolysis compared with heparin alone [mean control event rate (heparin only): 37 per 1000 patients; risk with additional thrombolysis: 25 per 1000 (95%CI from 14 to 45 per 1000)].
- Low quality evidence suggested that adjunctive thrombolysis increases the risk of major bleeding:
  - In 6 trials with 1,595 patients, there was a clinically important increase in intracranial haemorrhage [mean control event rate (heparin only): 12 per 10,000 patients; risk with additional thrombolysis: 73 per 10,000 (95%CI from 16 to 333 per 10,000)];
  - In 5 trials with 1,339 patients (Konstantinides 2002 was excluded due to heterogeneity), there was a clinically important increase in major extra-cranial bleeding [mean control event rate (heparin only): 120 per 10,000 patients; risk with additional thrombolysis: 500 per 10,000 (95%CI from 230 to 1080 per 10,000)].
- Low quality evidence from 2 trials and 190 patients suggested that thrombolysis is associated with a clinically important reduction in the risk of developing clinical symptoms that may predict CTEPH over the medium-term (3 and 28 months). Symptoms included persistent shortness of breath, reduced exercise capacity and echocardiographic evidence of elevated pulmonary artery systolic pressure [mean control event rate (heparin only): 421 per 1000 patients; risk with additional thrombolysis: 135 per 1000 (95%CI from 76 to 240 per 1000)].
- Low quality evidence from 1 trial of 83 patients showed that fewer survivors at 3 months who were treated with adjunctive thrombolysis reported poor quality of life (physical

functioning) compared with those treated with heparin alone, but there was uncertainty in the effect [mean control event rate (heparin only): 256 per 1000 patients; risk with additional thrombolysis: 28 per 1000 (95%CI from 2 to 200 per 1000)].

- Low quality evidence from 4 trials with 1,402 patients suggested that thrombolysis is associated with a clinically important reduction in the composite endpoint 'death or cardiopulmonary deterioration requiring treatment escalation' [mean control event rate (heparin only): 94 per 1000 patients; risk with additional thrombolysis: 41 per 1000 (95%CI from 27 to 63 per 1000)]
  - This effect is due to lower rates of cardiopulmonary deterioration;
  - For early mortality (within 7 days), data were inconclusive.
- For VTE-related mortality and recurrence of pulmonary embolism, data were inconclusive (very low quality evidence; up to 7 trials and around 1600 patients).

2.1.4.2 Health economic evidence statements

No economic studies were included in the literature review. The costs of thrombolysis medicines are greater than anticoagulation medicines.

2.1.5 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee agreed that all-cause mortality and major bleeding were key outcomes for assessing the efficacy and safety of thrombolysis in this patient population. It is also important to consider effects on VTE-related mortality although it was noted that low rates of autopsy mean, in practice, there is considerable under-diagnosis of death from pulmonary embolism. Concerns were expressed that the clinical composite outcome 'death or haemodynamic collapse / treatment escalation', commonly used as an endpoint in trials for statistical reasons, is not a meaningful outcome for clinicians or patients because avoidance of death would be more highly valued than avoidance of treatment escalation. Committee members sought clarification as to whether trials include treatment for non-fatal major bleeding in this composite endpoint; topic experts confirmed that treatment for non-fatal major bleeding is excluded from this composite outcome, which only includes additional treatment given in response to worsening haemodynamic / respiratory status. The Committee felt that use of the term 'cardiopulmonary deterioration' would avoid confusion when summarising the evidence for this composite endpoint. For the outcome 'VTE recurrence' few studies reported recurrent DVT, so only data for recurrent cases of PE were pooled in the analysis. The Committee agreed it is important to assess whether adjunctive thrombolysis confers benefits in terms of longer-term sequelae of non-fatal pulmonary embolism. Chronic thromboembolic pulmonary hypertension (CTEPH) carries a significant burden of morbidity and mortality. The lay topic expert highlighted the importance of quality of life as an outcome, because surviving a pulmonary embolism can impact significantly on patients' long-term physical, social and psychological wellbeing. Length of hospital stay is an important outcome in estimating resource use. The increased risk of bleeding associated with thrombolysis may necessitate a longer inpatient stay due to the requirement for closer monitoring or need for additional treatment and recuperation in the event of major bleeding.

	Committee discussions
Quality of evidence	The quality of evidence for all-cause mortality, VTE-related mortality and recurrence of PE was very low due to study limitations, indirectness of evidence and serious or very serious imprecision of effect estimates. The quality of evidence for major bleeding was low but the effect estimate was precise after removing one study from the analysis (Konstantinides 2002). The Committee agreed that use of 'rescue thrombolysis' in a relatively high proportion (23%) of control patients whose cardiopulmonary status deteriorated may explain the different pattern of major bleeding events observed in the Konstantinides study, and that removing the study from the meta-analysis was appropriate In the larger PEITHO trial (Meyer 2014), less than 5% of control group patients were given 'rescue thrombolysis'. High statistical heterogeneity in the initial analysis was reduced after the Konstantinides study was omitted. The resulting effect estimate was clinically significant, favouring heparin alone over heparin and adjunctive thrombolysis. Evidence for the composite outcome 'death or cardiopulmonary deterioration / treatment escalation' was low quality but the effect estimate was precise, favouring adjunctive thrombolysis over heparin alone. It was noted however that studies reporting this outcome used different criteria for determining cardiopulmonary deterioration and thresholds for treatment escalation. The Committee agreed that this reduces generalisability and interpretation of the effect estimate. Evidence for CTEPH was low quality due to very serious indirectness. The majority of studies included in the review had very short timeframes and none reported objectively confirmed cases of CTEPH. Evidence for this outcome comes from two small studies with patient follow-ups of 3 and 28 months respectively. The studies report clinical signs which a topic expert confirmed can only be considered surrogate indicators of CTEPH. For example, pulmonary artery systolic pressure ≥40 mm Hg (estimated via echocardiography in Sharifi et al. 2013) raises the possibility of pulmonary hypertension, but diagnosis requires a right heart catheter study. The baseline absolute risk for this outcome in the meta-analysis was about 42%; much higher than the 3-5% of patients that observational studies suggest will go on to develop confirmed CTEPH after a PE. Evidence on patient-reported quality of life was low quality due to serious indirectness and imprecision of the effect estimate. Only one small study reported quality of life, measured at 3 month follow-up using the SF-36. The Committee agreed that the narrow focus only on the 'physical functioning' component score of the SF36 was reductionist and limits the validity of the evidence. The effect estimate was uncertain with very wide confidence intervals due to small sample size. Length of stay was reported in one study (Sharifi 2013). The Committee agreed with the decision not to use these data in analyses. Concerns about the internal and external validity of the study mean the length of stay data reported are unlikely to be generalisable.
Trade-off between benefits and harms	The Committee considered there was clear evidence of harm associated with thrombolytic therapy in terms of increased risk of major bleeding. Intracerebral haemorrhage, in particular, has serious long-term implications for patient health and wellbeing.

	Committee discussions
	There was no clear evidence that thrombolysis confers a mortality benefit over standard anticoagulation alone. The Committee discussed that higher levels of patient monitoring in research trials may explain the relatively low overall rates of observed mortality (baseline risk: 3.7% compared with 3-15% suggested in the wider literature). Careful monitoring and early treatment of patients is likely to have been an important feature of the included studies. A topic expert confirmed that in practice up to 20% of patients with acute PE who are haemodynamically stable with RVD will experience cardiopulmonary deterioration (depending on definition). In Konstantinides (2002), 23% of the heparin-only group was given open-label 'rescue thrombolysis' after symptoms worsened. This occurred in less than 5% of the control group in Meyer (2014) due to stricter criteria for treatment escalation. The Committee agreed that for ethical reasons, it is likely that all studies included in the review gave 'rescue thrombolysis' to control group patients who deteriorated, although only 3 studies explicitly reported doing so. The observed effect of thrombolysis on mortality may be attenuated as a result. It was noted that the update remit was to compare initial treatment with standard anticoagulation and adjunctive thrombolysis versus standard anticoagulation only. The Committee agreed that thrombolysis given as a delayed 'rescue' treatment if patients deteriorate following a period of monitoring was outside the remit of the review and cannot form the basis of a recommendation as none of the studies was designed to explicitly address the effectiveness of monitoring and delayed thrombolysis in this patient population. Although the effect estimate did not cross the GRADE default MID of 0.75, the Committee were uncertain of the clinical significance of the observed reduction in early cardiopulmonary deterioration associated with thrombolysis (RR 0.44; 95%CI 0.29 to 0.67). Interpretation of this evidence is problematic due to differences between studies in definitions and criteria for triggering escalation of treatment (including giving rescue thrombolysis). Topic experts confirmed that the mechanism by which thrombolysis reduces early cardiopulmonary deterioration is via accelerated lung perfusion (when compared to heparin alone). However, observational studies show no between-group difference persists in lung perfusion or associated haemodynamic parameters by 7 days post-treatment. While evidence from the systematic review suggests there may be longer-term benefits associated with thrombolysis in terms of progression to CTEPH and patient-reported physical functioning, small numbers of studies and patients, indirectness of reported outcomes and very wide confidence intervals associated with the effect estimate reduces confidence in the data. Overall, the Committee considered the evidence for clinical benefits did not outweigh the evidence for harms associated with adjunctive thrombolysis in patients with acute PE who are haemodynamically stable with RVD.
Trade-off between net health benefits and resource use	No economic studies were included in the systematic review. Economic modelling was not required because the Committee decided that the clinical evidence alone did not support the use of thrombolysis in addition to anticoagulation for patients with PE and haemodynamic stability with right ventricular dysfunction.

	Committee discussions
	The Committee considered that thrombolysis incurs an additional cost to the NHS. Topic experts advised that the cost of additional resources required to monitor patients who had received thrombolysis would outweigh the additional cost of thrombolytic medicines themselves. In regards to long term consequences, cost savings may be available through the effective treatment of PE with thrombolysis. However, this may be offset or exceeded by the additional costs due to the risks associated with thrombolysis such as intracranial haemorrhage. Length of stay was reported by one of the studies included in the clinical systematic review (Sharifi 2013). This study found a lower mean length of stay of 2.2 days (SD 0.5) associated with thrombolysis compared with 4.9 days (SD 0.8) for anticoagulation alone. The Committee disregarded this finding because it was counterintuitive (a longer stay was expected for thrombolysis) and the mean length of stay for either treatment is below that experienced in the NHS (the average length of stay for pulmonary embolus ranges from 5 to 14 days according to the National Schedule of Reference Costs 2013-14 (HRG DZ09D/E/F/G) depending on severity). The mortality rate was unlikely to explain this difference found by Sharifi et al. because there was 1 death in the thrombolysis group and 3 in the anticoagulation only group. Overall, the Committee determined that thrombolysis in addition to anticoagulation for this population was likely to be associated with an increase in costs but no convincing evidence supporting an overall improvement in health.
Other considerations	A standing committee member questioned whether haemodynamically stable PE with RVD constitutes a narrow subgroup of patients whom it may be difficult to identify, and if there are equity issues regarding access to diagnostic testing. A topic expert stated that approximately 40% of patients presenting with acute PE are normotensive with signs of RVD, and that risk stratification to facilitate appropriate management is now accepted clinical practice. Ambulatory testing for RVD is possible (via ECG or blood tests for elevated levels of cardiac biomarkers) and most hospitals have access to CT pulmonary angiography, though fewer to immediate echocardiography. The key issue was noted as the lack of universally accepted parameters for diagnosing RVD with such tests. The Committee agreed that any recommendation to use thrombolysis for patients with RVD would therefore need to specify criteria for defining RVD. All studies included in the systematic review used heparin (either UFH or LMWH) for anticoagulation. Committee members noted that new oral anticoagulants (NOACs) such as apixaban and rivaroxaban are increasingly being used in the management of PE, without the need for preliminary heparin (https://www.nice.org.uk/guidance/ta287). The review protocol specified 'any standard accepted anticoagulant' as a comparator for adjunctive thrombolytic therapy but to date there are no published RCTs assessing effectiveness of thrombolysis in this patient population where NOACs are used for anticoagulation. The review protocol specified two subgroup analyses which could not be undertaken due to insufficient data, namely (i) lower-dose thrombolysis (versus standard dose), and (ii) catheter-directed (versus systemic) administration. Only one small open-label study included in the review used a lower dose of thrombolysis than that currently recommended for treating myocardial infarction and 'high risk' haemodynamically unstable PE. Topic experts noted that recent observational studies have shown that lower dose

	Committee discussions
	thrombolysis may have potential for reducing the risk of major bleeding associated with full dose systemic thrombolytic therapy. The Committee agreed that more RCT evidence using lower dose thrombolysis in this patient population would usefully inform any future update of this guideline. No studies that used catheter-directed (as opposed to systemic) administration of thrombolysis met the review protocol inclusion criteria. Topic experts noted that NICE interventional procedures guidance has recently been published on ultrasound-enhanced catheter-directed thrombolysis (UE-CDT; http://www.nice.org.uk/Guidance/IPG524); however for the purpose of this update, pharmacomechanical methods of thrombolysis were outside the review remit. The Committee considered the subgroup analyses that had been undertaken to compare effects in studies using tenecteplase versus alteplase, and in younger- versus older-age patients. There was agreement that these analyses had too many caveats for conclusions to be confidently drawn. It was noted that tenecteplase is not currently licensed for the treatment of PE. Currently there is insufficient evidence of longer-term benefits on which to base a recommendation for use of thrombolysis. However, it was noted that the largest of the included RCTs, the PEITHO trial (Meyer et al. 2014), has not yet reported a 6-month follow-up of patients. The planned follow-up will include assessment of clinical outcome, functional status and severity of dyspnoea (using the New York Heart Association scale), and echocardiographic estimates of pulmonary artery systolic pressure and RVD. This will provide more robust evidence of the effects of thrombolysis on the progression to CTEPH, which will inform a future update of this guideline. After discussing the evidence, the Committee decided not to recommend thrombolytic therapy for patients with acute PE who are haemodynamically stable and have right ventricular dysfunction. The Committee agreed there was no justification for exposing this population of patients to the increased risk of major bleeding associated with adjunctive thrombolysis considering the lack of evidence of a clear reduction in mortality, uncertain clinical importance of the observed reduction in short-term cardiopulmonary deterioration and insufficient evidence of longer-term health benefits. If patients' cardiopulmonary status should subsequently deteriorate, baseline mortality risk may increase. Clinicians should re-assess, on an individual patient basis, the risk:benefit ratio of giving thrombolysis to patients who become haemodynamically unstable following standard anticoagulation treatment.

2.1.6 Recommendations

1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), taking into account comorbidities, contraindications and drug costs, with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT

(activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.

- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism).

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer. [2012]

1.2.7 Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). [2012]

1. Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability with or without right ventricular dysfunction (see also recommendation 1.2.1 on pharmacological interventions for DVT and PE). If patients develop haemodynamic instability, see recommendation 1.2.7 [New 2015]

2.1.7 Research recommendations

Thrombolysis for patients with acute PE and right ventricular dysfunction

1. Does thrombolysis in patients with acute PE and right ventricular dysfunction (RVD) improve long- term quality of life and /or reduce the incidence of chronic thromboembolic pulmonary hypertension (CTEPH)? [New 2015]

Why is this important?

PE may affect patients' long-term quality of life and functional capacity. Because of the short timeframes of previous studies, there is currently insufficient evidence to determine whether thrombolysis confers additional longer-term benefits compared with anticoagulation alone in patients with acute PE who are haemodynamically stable with right ventricular dysfunction.

Table 3: Research recommendation 1: criteria for selecting high-priority research recommendations

PICO	**Population**: Haemodynamically stable patients with acute PE and objective evidence of RVD (measured on CTPA/echocardiogram/ECG/biomarkers). **Intervention:** Thrombolysis with standard anticoagulation. **Comparison:** Standard anticoagulation alone or with placebo. Rescue thrombolysis for patients who develop haemodynamic instability. **Outcomes:** Quality of life; exercise capacity; persistent shortness of breath after at least 3 months of therapeutic anticoagulation; CTEPH up to 2 years

Current evidence base	Kline et al. (2014) suggest that thrombolysis compared to standard anticoagulation in patients with RVD may be associated with improvement in medium- to long-term functioning and patient-reported quality of life. Pengo et al. (2004) and other prospective observational studies have reported that up to 5% of those who survive a PE may go on develop CTEPH within 2 years. CTEPH results in significant morbidity and mortality. Previous PE, thrombus burden, sPAP >50mmHg at the time of the index PE are associated with the diagnosis of CTEPH during follow up. Serial echocardiographic measures of systolic pulmonary artery pressure (sPAP) in patients treated with thrombolysis compared to standard anticoagulation show greater improvement in sPAP (Sharifi et al., 2013).
Study design	RCT

2. Does lower-dose thrombolysis reduce the risk of major bleeding and improve outcomes in patients with acute PE and right ventricular dysfunction?

Why is this important?

The narrow benefit-to-risk ratio of thrombolysis is due to the associated bleeding risks. Excluding any shunts, the lungs generally receive the entire cardiac output, and a lower dose of thrombolysis may be enough to treat PE with a lower risk of bleeding.

Table 4: Research recommendation 2: criteria for selecting high-priority research recommendations

PICO	**Population**: Haemodynamically stable patients with acute PE and objective evidence of RVD (measured on CTPA/echocardiogram/ECG/biomarkers). **Intervention:** Low-dose thrombolysis with standard anticoagulation. **Comparison:** Standard anticoagulation alone or with placebo. Full dose thrombolysis with standard anticoagulation (optional). Rescue thrombolysis for patients who develop haemodynamic instability. **Outcomes:** Major bleeding using standard definitions; treatment escalation not due to bleeding (including inotropes, CPR, ventilatory support); mortality; VTE recurrence; Quality of life; exercise capacity; persistent shortness of breath after at least 3 months of therapeutic anticoagulation; CTEPH up to 2 years.
Current evidence base	Sharifi et al. (2013) reported that a strategy of lower dose thrombolysis in "moderate PE" appeared to be safe. Wang et al. (2010) showed that regimens of 50 mg or 100 mg rt-PA exhibited similar efficacy in patients with acute PE and either haemodynamic instability or with massive pulmonary artery obstruction.
Study design	RCT

2.2 Review question 2: Compression stockings for PTS prevention

2.2.1 Review question

What is the effectiveness of stockings to prevent post-thrombotic syndrome in people with confirmed proximal deep vein thrombosis?

2.2.2 Clinical evidence review

A systematic search was conducted (see Appendix D.2.1) which identified 1153 articles. The titles and abstracts were screened and 33 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C.2). Of these, 29 were excluded as they did not meet the criteria and 4 met the criteria and were included. A summary of the included studies is presented in Table 5.

A review flowchart is provided in Appendix E.1.2, and the excluded studies (with reasons for exclusion) are shown in Appendix F.2.

Methods

Outcomes were chosen and prioritised by the topic experts, and reviewed by core Committee members before the review was undertaken. PTS (incidence and/or severity) and adherence were chosen as critical outcomes for decision making. The following outcomes were considered important for decision making: quality of life, VTE recurrence, VTE-related mortality, adverse skin events.

Where more than one study assessed a specified outcome for a given comparison, the data were combined using a pair-wise meta-analysis. Forest plots from the meta-analyses are in Appendix I.2.

A random effects model was used for the dichotomous outcomes included. The random effects model was chosen in consideration of the possible distribution of the effects of the intervention as there were varying criteria used for PTS across the studies and it is likely that there may have been differences in the study participants. Tau^2 was used to consider heterogeneity (>1.0 used as a threshold for statistical heterogeneity to downgrade).

All of the included studies were randomised controlled trials. The quality of evidence for the each outcome for each comparison (where there was evidence available) was considered using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group. There was not data available from the included studies to include any of the subgroups that had been identified in the review protocol.

A routine search of the Core Outcome Measures in Effectiveness Trials (COMET Initiative) database did not yield information on accepted minimum clinically important difference thresholds (MIDs) for any of the outcomes under consideration in this review and no published MIDs were found in a search of the medical literature. The minimum clinically important differences used were those from the GRADE default, (RR=0.75 and 1.25 for dichotomous outcomes). Consideration of previous guidelines and other relevant publications had not yielded any other suggested minimum clinically important differences, following discussion with the topic experts it was agreed that the GRADE default would be used.

For the full evidence tables and GRADE profiles please see Appendices G and H.

Table 5: Summary of included studies for Review Question 2: Compression stockings for the prevention of post-thrombotic syndrome in people with confirmed proximal DVT

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
Brandjes et al. (1997) RCT The Netherlands	N=194 After first episode of proximal DVT	Below-knee elastic compression stockings applied 2 to 3weeks after first episode of DVT compared with no stockings	• Cumulative incidence of mild-to-moderate PTS • Severe PTS • Recurrence of VTE • Venous ulceration • Compliance	N/A
Prandoni et al. (2004) RCT Italy	N=180 Clinically symptomatic proximal DVT	Below-knee elastic compression stockings applied at hospital discharge (average 1week after admission) compared with no stockings	• Cumulative incidence of PTS • Recurrence of VTE • Adverse effects • Adherence	N/A
Kahn et al. (2014) RCT Canada, USA	N=806 First proximal DVT	Below-knee elastic compression stockings applied within 2weeks of DVT diagnosis compared with placebo stockings	• Cumulative incidence of PTS • Recurrent VTE • Recurrent DVT • Leg ulcers • Death • Stocking use • Adverse events	N/A
Aschwanden et al. (2008) RCT Switzerland	N=169 First or recurrent proximal DVT	Below-knee elastic compression stockings applied at the end of 6months standard DVT therapy compared with no stockings	• Occurrence of PTS skin changes • PTS associated symptoms • Adherence	The 6 months standard therapy included the use of compression stockings

2.2.3 Health economic evidence review

2.2.3.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review question. The evidence was identified by conducting a broad search in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 7 April 2015. The health economic search strategy is detailed in Appendix D.2.2.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence. Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.2.3.2 Results of the economic literature review

382 articles were retrieved by the database search. All of these were excluded based on title and abstract. Therefore, no relevant economic studies were included in the systematic review.

2.2.4 Evidence statements

2.2.4.1 Clinical evidence statements

Four trials reported data on the incidence of PTS during follow-up. Three trials were included in a meta-analysis, with 1174 participants, considered stocking use compared with no stockings or placebo stockings following diagnosis of proximal DVT (very low quality evidence). This did not show a difference between the stocking use and no stockings/placebo stocking use groups (RR 0.64; 95% CI 0.37 to 1.12). One trial with 169 participants considered stocking use compared with no stocking use after 6 months of initial DVT treatment (very low quality evidence). This trial did not show a difference between stocking use and no stocking use for the development of post thrombotic skin changes (surrogate marker for PTS).

Three trials reported rates of recurrent VTE during follow-up. These three trials were included in a meta-analysis, with 1174 participants considered stocking use compared with no stockings or placebo stockings (very low quality evidence). This did not show a difference between the groups (RR 0.91; 95% CI 0.65 to 1.27).

Four trials considered adherence/compliance with stocking use during the trials. They used differing methods of self-reporting (very low quality evidence). Three trials comparing stockings with no stockings showed levels of adherence/compliance with stocking use that were >75%. One trial of stocking compared with placebo stocking showed that stocking use for 3 or more days per week decreased from 83-89% at 1 month to around 55% at 24 months.

One trial (very low quality evidence) reported small numbers of rash or itching in both the group wearing stockings (N=8/409) and the groups wearing placebo stockings (N=7/3894).

2.2.4.2 Health economic evidence statements

No studies were included in the economic literature review. The cost of stockings ranges from £16 to £30 per pair.

2.2.5 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee agreed that to consider the effectiveness of elastic, graduated, compression stockings the clinical outcomes that would provide the most benefit to their decision making would be PTS incidence, VTE recurrence, quality of life and adverse skin events. Within the consideration of outcomes the committee discussed the adherence, noting that this has the potential to have a substantial impact on the effectiveness of the stocking use. As the stockings apply a pressure to the leg they may be uncomfortable, itchy or warm to wear. They are also given for long-term use. These factors may affect adherence to their use. The committee noted that PTS is a chronic condition with a variety of signs and symptoms that may develop over time which can make clinical diagnosis difficult. The committee discussed the variability in the PTS criteria used for diagnosis in PTS in the included studies, that PTS diagnosis involves both objective and subjective measures. Furthermore the

	Committee discussions
	topic experts considered that skin changes, such as venous ulceration, could be used as a potential surrogate marker for severe PTS. They considered that this outcome should be treated separately from other skin related outcomes that may be related to the stocking use such as itching. The committee considered the importance of patient quality of life outcomes as PTS is a chronic, potentially difficult to treat condition.
Quality of evidence	The committee discussed the inclusion of the study (Aschwanden, 2008) where participants were not recruited onto the study after initial DVT treatment (as they had been in the other studies) but were recruited following 6 months of DVT treatment. The committee considered that this may be an appropriate use of stockings, as it may be appropriate to assess patients who have had a proximal DVT after 6 months and consider stocking use again at this point. Therefore this study was included in the evidence review alongside the 3 other studies where participants were recruited following proximal DVT diagnosis (2 to 3 weeks after diagnosis or at hospital discharge). The committee discussed the considerable heterogeneity of the included studies, noting that studies had used different comparators. Three of those included studies had used no stockings as a comparator and the other included study had used placebo stockings. . The committee considered the use of the placebo stocking and discussed whether this may have had an impact on the outcomes of the study as some elastic compression will have been exerted. Though they did note that the use of this placebo had enabled the study to be blinded and account for the placebo effect. This was not possible in the open-label studies. Topic experts considered that if the pressure applied by compression stockings from different manufacturers was similar, then the use of stockings from different manufacturers across studies should not have an impact on the outcomes. The committee discussed the importance of ensuring good fit of the stockings used and that this was not reported in some of the included studies. The committee noted that if the stockings are not correctly fitted then this could reduce their possible effectiveness. The committee agreed that, while acknowledging the heterogeneity of the studies, it was appropriate to meta-analyse the reported data on PTS incidence and VTE recurrence from the studies that had commenced following DVT diagnosis. The committee agreed that the data from the study that had commenced following 6 months of initial treatment should not be included in the meta-analysis. The committee members noted that there was considerable divergence in the PTS incidence between the studies. The differences in methodology used in the trials in the meta-analysis were discussed; two trials were single-centred and open-label and the other trial was a larger, multi-centre, blinded, placebo controlled trial. Accepting these differences the committee further discussed the potential impact that adherence may have had on the outcomes of these trials. They discussed the uncertainty that the self-reporting and inconsistent measurement of this gives to the outcomes. The committee discussed the collection of the adherence data used within the studies. It was noted that the Kahn (2014) study showed reduction in adherence with both intervention and placebo stockings throughout the 24months of the study. The committee discussed the importance of

	Committee discussions
	adherence and discussed whether the use reported in this study may be reflective of the real life experience of those wearing stockings. Furthermore the level of adherence that may be required to detect any possible difference in the PTS incidence is not known. The included studies provided an arbitrary indication of what was considered to be sufficient (such as wearing for greater than a certain number of days per week being considered reasonable adherence). Where adherence had been reported regularly throughout the study time frame (accepting the discussions about whether or not the ≥3 days/week use is sufficient) it was noted that adherence decreased from over 85% at 1 month to around 55% at 24 months for both the intervention and placebo stocking groups. The committee noted that there were few data reported on the skin effects of the stockings and adverse effects. The limited available evidence on these outcomes did not suggest that wearing stockings had caused any adverse effects for patients. They further noted the lack of quality of life outcomes in the included studies and agreed that these may provide useful data in any future study.
Trade-off between benefits and harms	The committee noted that all of the included evidence related to knee-length stockings, therefore recommendations could not be made for any other stocking length. The committee agreed that the available evidence did not show a benefit in PTS prevention or the prevention of VTE recurrence with the use of the graduated elastic compression stockings. The committee agreed that not recommending the stockings for these preventative uses was appropriate and consistent with the evidence provided in the included studies. The committee considered that there may be potential benefits for those with leg symptoms following their proximal DVT, that the stockings may provide some symptom relief. The committee discussed the possibility that patients have been using the stocking to provide symptom relief, as well as for the possible prevention of PTS, and were concerned that stopping using stocking would be detrimental to the symptom relief. The use of stockings for symptom relief is not within the scope of this guideline update. The committee concluded that it was important to be clear that the review question included in this guideline update related specifically to the preventative aspect of stocking use and not any role that stockings may have for leg symptom relief. Therefore the committee agreed that noting within the recommendation that it was specifically relating to stocking use as a preventative measure and not for any leg symptoms would ensure clarity for the guideline users.
Trade-off between net health benefits and resource use	No economic studies were included in the literature review. Economic modelling was not required because the Committee determined that the quality of clinical evidence was not sufficient to populate a model. Topic experts advised that the cost of stockings in secondary care ranged from £16 to £30 per pair. One pair lasts a patient for 6 months, one stocking being worn on the affected leg for 3 months. Compression stockings represent an additional cost to the NHS which is not offset by preventing PTS based on the clinical evidence considered in this update. Therefore, cost savings are available by ceasing to use compression stockings for the prevention of PTS. The use of compression stockings for the treatment of leg symptoms was outside the scope of this update.
Other considerations	In consideration of the evidence presented to the committee and detailed discussions by them, the committee agreed that the available evidence did not support the use of graduated, elastic, compression stockings for the

	Committee discussions
	prevention of PTS or the prevention of VTE recurrence. The committee noted that these stocking are used by some patients for leg symptoms following their proximal DVT. The committee discussed the potential benefit to patients of this use and therefore recommended that the compression stockings should not be offered for the preventative uses but that the recommendation should be clear that this does not cover use for leg symptoms.

2.2.6 Recommendations

2. Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or for the prevention of venous thromboembolic disease recurrence after a proximal deep vein thrombosis (DVT). This recommendation does not cover the use of elastic graduated compression stockings for the management of leg symptoms after DVT. [New 2015]

2.2.7 Research recommendations

3. What is the effectiveness of stockings, when adherence is adequate, for preventing post-thrombotic syndrome in people with confirmed, proximal deep vein thrombosis? [New 2015]

Why is this important?

While there have been trials of elastic graduated compression stockings for preventing PTS following proximal DVT, there are aspects of these studies that make it difficult to be certain about the outcomes. In addition, these studies have differed considerably on whether or not the use of these stockings is effective. The Committee noted the importance of ensuring adherence in research on any possible preventative role of elastic compression stockings.

The committee concluded that the currently available evidence does not aid decision making, due to the uncertainty of the output.

Table 6: Criteria for selecting high-priority research recommendations

PICO	Population: adults with confirmed DVT(where adherence to stocking use can be objectively measured) Intervention: graduated elastic compression stockings (Subgroups; differing types of DVT; use starting just after DVT presentation or after patient review at 6months) Comparison: placebo stockings or no stockings Outcomes: post-thrombotic syndrome incidence, adherence, quality of life
Current evidence base	Current evidence shows inconsistent results relating to stocking use for PTS prevention in those who have had a confirmed proximal DVT. Adherence to the intervention has not been sufficiently reported or has been unclearly measured. The limitations with the criteria used to consider sufficient adherence with use and the reporting of this mean that there is considerable uncertainty in this evidence.
Study design	RCT

Other comments

3 References

Aschwanden M, Jeanneret C, Koller MT et al. (2008) Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. Journal of Vascular Surgery 47:1015-21

Becattini C, Agnelli G, Salvi A et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125: e82-e86.

Belohlavek J, Dytrych V, Linhart A. (2013) Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and non-thrombotic pulmonary embolism. Experimental and Clinical Cardiology 18: 129-138.

Brandjes DPM, Buller HR, Heijboer H et al. (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 349:759-62

Fasullo S, Scalzo S, Maringhini G et al. (2011) Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341: 33-9.

Goldhaber SZ, Haire WD, Feldstein ML et al. (1993) Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 341: 507-11.

Kahn SR, Shapiro S, Wells PS et al. (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 383:880-88

Kline JA, Nordenholz KE, Courtney DM et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. Journal of Thrombosis and Haemostasis 12: 459-68.

Kline JA, Hernandez J, Hogg MM et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia : EMA 25: 515-26.

Konstantinides S (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. American Heart Journal 163: 33-38.e1.

Konstantinides S, Geibel A, Heusel G et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. The New England Journal of Medicine 347: 1143-50.

Meyer G, Vicaut E, Danays T et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. The New England Journal of Medicine 370: 1402-11.

Pengo V, Lensing A, Prins M, et al. (2004) Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. New England Journal of Medicine 350: 2257-64

Prandoni P, Kahn S. (2009) Post-thrombotic syndrome: prevalence, prognostication and need for progress. British Journal of Haematology 145: 286 - 295

Prandoni P, Lensing AWA, Prins MH et al. (2004) Below-knee elastic compression stockings to prevent the post-thrombotic syndrome. Annals of Internal Medicine 141:249-256

Sharifi M, Bay C, Skrocki L et al. (2013) Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). The American Journal of Cardiology 111: 273-7

Wang C, Zhai Z, Yang Y, Wu Q, Cheng Z., et al. (2010) Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest 137: 254-262

4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below.

Anticoagulant: Treatment to prevent the formation of blood clots, including oral agents (e.g. warfarin) and others injected into a vein or under the skin (e.g. heparin).

Calf vein DVT, distal DVT: A DVT which involves the veins of the calf but not higher veins. See 'proximal DVT'.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH): A long-term complication of non-fatal PE

Continuation phase (of anticoagulation treatment): The phase of anticoagulation treatment after the initial phase. This is usually with VKA treatment, though LMWH may be used particularly in cancer patients. See also 'initial phase of treatment'

Graduated compression stockings (GCS) or hosiery: Supportive stockings designed to facilitate compression therapy, a technique that helps improve circulation to relieve a range of medical conditions such as varicose veins or DVT depending on the pressure applied at the ankle.

Haemodynamically stable PE: When a patient with PE also has a normal blood pressure. The haemodynamically stable patient subgroup will include groups previously referred to as normotensive, non-massive, or sub-massive PE. Within this group there are two subgroups of patients that may be considered separately by clinicians, according to whether there is evidence of right heart strain or injury. See also 'pulmonary embolism'.

Haemodynamically unstable PE: when a patient with PE also has a low blood pressure defined by a systolic blood pressure < 90mmHg or a pressure drop of ≥40 mmHg for >15 minutes if not caused by an arrhythmia, hypovolaemia or sepsis. The haemodynamically unstable patient subgroup will include groups previously referred to as massive PE.

Initial phase (of anticoagulation treatment): The period from the confirmation of VTE diagnosis until the continuation phase of treatment is established. See also 'continuation phase of treatment'.

Major bleeding: Bleeding that is overt and has one or more of the following characteristics: a decrease in haemoglobin concentration by at least 2.0g/dL; the need for transfusion of at least 1-2 units of blood; intracranial or retroperitoneal bleeding; caused an interruption of therapy; or led to death.

Thrombolytics / thrombolysis: Pharmacological agents/drugs such as streptokinase, urokinase and recombinant tissue-type plasminogen activator (rt-PA) used in the treatment of VTE to actively break up clots leading to rapid normalisation of vascular blood flow.

Post-thrombotic syndrome (PTS): The chronic pain, swelling, and occasional ulceration of skin on the leg that occurs as a consequence of previous venous thrombosis.

Proximal DVT: DVT in the popliteal vein or above. Proximal DVT is sometimes referred to as 'above-knee DVT'

Right ventricular dysfunction (RVD) Acute PE may lead to right ventricular pressure overload and dysfunction, which can be detected by echocardiography, CT pulmonary angiography (CTPA) or elevated biomarkers due to myocardial stretch (e.g. brain natriuretic peptide) or transmural RV infarction (cardiac troponin). Combinations of these indices may be used for risk stratification.

Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV/LV diameter ratio; hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On four-chamber views of the heart by CTPA, RV enlargement defined by an increased end-diastolic RV/LV diameter ratio (with a threshold of 0.9 or 1.0) may be an indicator of RV dysfunction.

Pulmonary embolism: A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries, causing severe respiratory dysfunction.

Systemic thrombolysis: A thrombolytic agent (for example streptokinase) that reaches the target thrombus via the systemic circulation

Vitamin K antagonist (VKA): An oral treatment that inhibits vitamin K thus preventing coagulation. These include coumarins, such as warfarin, and phenindione.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Susan Bewley (Chair)	Professor of Complex Obstetrics, Kings College London
Gita Bhutani	Clinical Psychologist, Lancashire Care NHS Foundation Trust
Simon Corbett	Cardiologist, University Hospital Southampton NHS Foundation Trust
John Graham	Consultant Oncologist & Trust Cancer Lead Clinician, Taunton & Somerset Hospital
Peter Hoskin	Consultant in Clinical Oncology, Mount Vernon Hospital
Roberta James	Programme Lead, Scottish Intercollegiate Guidelines Network (SIGN)
Jo Josh	Lay member
Asma Khalil	Obstetrician, St George's Hospital University London
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist, University of Sheffield
Mark Rodgers	Research Fellow, University of York
Nicholas Steel	Clinical Senior Lecturer in Primary Care, Norwich Medical School
Sietse Wieringa	General Practitioner, Barts & the London School of Medicine & Dentistry

A.2 Topic expert committee members

Name	Role
David Fitzmaurice	GP, Birmingham University
Hayley Flavell	Thrombosis nurse, Royal Bournemouth Hospital Foundation Trust
Karen Sheares	Consultant Respiratory Physician, Papworth Hospital NHS Foundation Trust
Gerard Stansby	Professor of Vascular Surgery, Freeman Hospital, Newcastle
Paul Westerman	Lay member

Name	Role
Martin Allaby	Clinical Advisor
Jessica Fielding	Public Involvement Advisor
James Hall	Senior Medical Editor
Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager
Sharon Summers-Ma	Guideline Lead
Judith Thornton	Technical Lead
Trudie Willingham	Guideline Co-ordinator

A.3 NICE project team

A.4 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Jenny Craven	Information Specialist
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Nicki Mead	Technical Analyst
Rebecca Parsons	Project Manager
Charlotte Purves	Administrator
Roberta Richey	Technical Analyst
Toni Tan	Technical Advisor

Appendix B: Declarations of interests

Member name	Interest declared	Type of interest	Decision
Susan Bewley	Self-employed academic and obstetric expert.	Personal financial interest	Declare and participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics)	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for external reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review)	Personal financial interest	Declare and participate
Susan Bewley	Received fee for Chairing NICE GDG	Personal financial interest	Declare and participate
Susan Bewley	Received royalties from edited books	Personal financial interest	Declare and participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	Personal non-financial interest	Declare and participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and “for treatments that work”) and a	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
	trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).		
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, Journal Article Summary Service; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women's Health and Equality Consortium which is a Strategic Partner of the Department of Health.	Personal non-financial interest	Declare and participate
Susan Bewley	Part-time on call sexual offences examiner (forensic medical examinations) working at the Haven Camberwell Sexual Assault Referral Centre (Kings College Hospital)	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee as Consultant for the World Health Organisation (five days approx), for their updated guideline on Reproductive and Sexual Health and Human Rights for Women living with HIV	Personal financial interest	Declare and participate
Susan Bewley	Received fee as Chair of NICE Fertility Evidence Update	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee as External examiner obstetrics and gynaecology, University College Dublin	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for maternal mortality investigation	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for RCOG service review Independent Review panel	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for medicolegal criminal case	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for obstetric and managerial advice (overseas not- hospital) for-profit	Personal financial interest	Declare and participate
Susan Bewley	Received fee for attending NICE GRADE training development	Personal financial interest	Declare and participate
Susan Bewley	Received fee for appearances on BBC Radio 4 (inside health, in the ethics committee)	Personal financial interest	Declare and participate
Susan Bewley	Received fee for lecture at Royal Society of Medicine Retired Fellows Modern Reproduction: blood, guts, loss and King Midas	Personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Susan Bewley	Expenses paid to lecture at the National RCOG trainees annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the Royal Society of Medicine	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the GLADD Annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the FIL Annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the RCOG Review training	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the BPAS Annual Meeting Clinical Forum	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the WOW Festival	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lectures relating to publicising NICE intrapartum guidelines	Personal non-financial interest	Declare and participate
Susan Bewley	Lecture fee, at 'safe hands conference' Bolton	Personal financial interest	Declare and participate
Susan Bewley	Unpaid (but travel, hotel and subsistence) trip to two not-for-profit maternity hospitals in return for four days teaching/ expert advice, India	Personal financial interest	Declare and participate
Gita Bhutani	Chair of Psychological Professions Network North West	Personal non-financial interest	Declare and participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	Personal non-financial interest	Declare and participate
Gita Bhuitani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	Personal non-financial interest	Declare and participate
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safety	Personal non-financial interest	Declare and participate
Gita Bhutani	Joint project lead on Health Education North West funded project on Schwartz Rounds	Personal, non-financial, non-specific	Declare and participate
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Simon Corbett	Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of this role involves the dissemination and implementation of NICE guidance in the Trust.	Personal non-financial interest	Declare and participate
Simon Corbett	Independent cardiologist on the Trial Steering Committee of the randomised controlled AVATAR trial, a randomised trial of medical therapy vs ablation in patients with atrial fibrillation. The study is sponsored by Imperial College London and is part funded by Medtronic. Travel expenses are paid by Imperial.	Personal non-financial interest	Declare and participate
Gail Fortes Mayer	None		Declare and participate
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	Non-personal financial interest	Declare and participate
John Graham	Principal investigator for On-going clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer Pharmaceuticals	Non-personal financial interest	Declare and participate
John Graham	Principal investigator for 8 On-going clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	Non-personal financial interest	Declare and participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	Personal non-financial interest	Declare and participate
John Graham	Consultancy work for NICE International on a project with the Philippines Department of Health to produce clinical guidelines on breast cancer. Travel expenses paid	Personal non-financial interest	Declare and participate
John Graham	Council member of the South-West England Clinical Senate	Personal non-financial non specific	Declare and participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.	Non-personal financial interest	Declare and participate
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	Personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the Steering Group for National Cancer Intelligence Network (NCIN)	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Personal non-financial interest	Declare and participate
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the East of England senate.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member European Society for Radiotherapy and Oncology (ESTRO) Board	Personal non-financial interest	Declare and participate
Peter Hoskin	Member HTA Clinical Evaluation and Trials Board	Personal non-financial interest	Declare and participate
Peter Hoskin	Clinical Editor, radiotherapy and Oncology	Personal non-financial interest	Declare and participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network	Personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Roberta James	Member of Guideline Implementability Research and Application network	Personal non-financial interest	Declare and participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health	Personal non-financial interest	Declare and participate
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	Personal non-financial	Declare and participate
Asma Khalil	Co-chair of the “Improving Outcomes” working group, South West London Maternity Network	Personal non-financial	Declare and participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	Personal non-financial	Declare and participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	Personal non-financial	Declare and participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	Personal non-financial	Declare and participate
Asma Khalil	Principal Investigator at St George’s Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	Personal non-financial	Declare and participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in Symptomatic women (QFCAPS)	Personal non-financial	Declare and participate
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	Personal non-financial	Declare and participate
Asma Khalil	Reviewer for the National Maternal Near-miss Surveillance Programme	Personal non-financial	Declare and participate
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Research Authority, London	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Quality Improvement Partnership, London	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	Personal non-financial interest	Declare and participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: ‘Transition between inpatient hospital settings and community or care home settings for adults with social care needs.’	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Manoj Mistry	Lay representative for the MSc Clinical Bioinformatics at the University of Manchester	Personal non-financial interest	Declare and participate
Manoj Mistry	Lay Educational Visitor with the Health and Care Professions Council, London	Personal non-financial interest	Declare and participate
Manoj Mistry	Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS FT/University of Manchester)	Personal non-financial interest	Declare and participate
Manoj Mistry	Public Representative Interviewer at the Medical School, Lancaster University	Personal non-financial interest	Declare and participate
Manoj Mistry	Public Member of NIHRs 'Research for Patient Benefit Programme Committee' (North West region)	Personal non-financial interest	Declare and participate
Manoj Mistry	Member of the Patient Panel at NIHRs 'The Collaboration for Leadership in Applied Health Research and Care' Greater Manchester	Personal non-financial interest	Declare and participate
Manoj Mistry	Member of the Patient and Public Involvement Group, Liverpool Clinical Trials Unit, University of Liverpool	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI panel assisting research into Information Systems: Dashboard: Monitoring and Managing from Ward to Board at the University of Leeds	Personal non-specific non-financial	Declare and participate
Manoj Mistry	Member of the Study Steering Committee for the research project: ''Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC): a study of the implementation and effectiveness of a new model of care for long term conditions ''(University of Manchester/ Salford Royal).	Non-specific non-personal	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	Personal financial interest	Declare and participate
Amaka Offiah	Recipient of honoraria and expenses for lectures and guidelines development from BioMarin.	Personal financial interest	Declare and participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	Personal non-financial interest	Declare and participate
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Paediatric Radiology.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and Scoliosis.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of South Yorkshire (Sheffield) Research Ethics Committee.	Personal non-financial interest	Declare and participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA	Personal non-financial interest	Declare and participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield)	Personal non-financial interest	Declare and participate
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology	Personal non-financial interest	Declare and participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	Non-personal financial interest	Declare and participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	Personal non-financial	Declare and participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	Personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	Non-personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group reports and Technology Assessment Reports as part of the NICE technology appraisals process.	Non-personal financial non-specific	Declare and participate
Nicholas Steel	Work as the principal investigator on a National Institute of Health Research funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary care?'	Non-personal financial interest	Declare and participate
Nicholas Steel	National Institute for Health Research Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	Personal non-financial interest	Declare and participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for Patient Benefit Programme East of England region	Personal non-financial interest	Declare and participate
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	Personal non-financial interest	Declare and participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards East of England	Personal non-financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Nicholas Steel	'Implementation Science' Editorial Board member	Personal non-financial interest	Declare and participate
Nicholas Steel	'Quality in Primary Care' Editorial Board member	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	Personal non-financial interest	Declare and participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	Personal non-financial interest	Declare and participate
Nicholas Steel	Publication in press: Steel N, Abdelhamid A, Stokes T, Edwards H, Fleetcroft R, Howe A, Qureshi N. Publications cited in national clinical guidelines for primary care were of uncertain relevance: literature review. In Press Journal of Clinical Epidemiology	Personal non-financial interest	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen Mary University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	Personal financial interest	Declare and participate
Sietse Wieringa	I co-own a small social enterprise called ZorgIdee that develops ideas to help GPs to collaborate. There are no current funders.	Personal financial interest	Declare and participate
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	Non-personal financial interest	Declare and participate
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	Personal non-financial interest	Declare and participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	Personal non-financial interest	Declare and participate
Topic expert	**Interest declared**	**Type of interest**	**Decision**
Gerard Stansby	None	n/a	Declare and participate

Member name	Interest declared	Type of interest	Decision
Karen Sheares	Received support from Bayer and Actelion for registration, travel and accommodation to attend meetings and conferences.	Personal financial non-specific	Declare and participate
Karen Sheares	Member of the British Thoracic Society Guideline Group for the Ambulatory Management of Pulmonary Embolism.	Personal, non-financial, non-specific	Declare and participate
Paul Westerman	None	n/a	Declare and participate
David Fitzmaurice	None	n/a	Declare and participate
Hayley Flavell	Leading change to improve stroke prevention outcomes for patients with Non-Valvular AF Advisory Board for BMS/Pfizer.	Personal, financial, non-specific	Declare and participate
Hayley Flavell	Leading Excellence for Stroke Prevention Masterclass funded by BMS/Pfizer	Personal, financial, non-specific	Declare and participate
Hayley Flavell	Presentation at Pradaxa & Presentation for Boehringher Ingelheim	Personal, financial, non-specific	Declare and participate

Appendix C: Review protocols

C.1 Review question 1: Thrombolysis for PE

	Details
Review Question	What is the effectiveness of thrombolysis given in addition to standard accepted anticoagulation therapy compared with anticoagulation therapy alone in patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction?
Objectives	Thrombolysis, given in addition to standard anticoagulation, is recommended in NICE CG144 for patients with high-risk acute PE who are haemodynamically unstable. However it was not possible to determine whether additional thrombolytic therapy confers benefits for patients with intermediate-risk PE. This subgroup of patients, who present with right ventricular dysfunction (RVD) but are haemodynamically stable, could not be distinguished from patients with low-risk PE (haemodynamically stable with no RVD) in the evidence that was available during development of the original guideline. Consequently, a research recommendation was made. The recent surveillance review of CG144 highlighted that new evidence is now available in relation to thrombolysis for intermediate-risk PE. The review aims to assess the clinical and cost-effectiveness and safety of thrombolysis given in addition to standard anticoagulation compared with anticoagulation treatment alone in this subgroup of patients.
Type of Review	Intervention
Language	English only
Study Design	Randomised controlled trials (RCTs), systematic reviews of RCTs Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook
Status	Published papers (full text only)
Population	Adults (18+) with acute confirmed PE who are normotensive and have objective evidence of RV dysfunction, as follows: - reported abnormality on echocardiogram or CT pulmonary angiogram, *or* - abnormalities of cardiac biomarkers (troponin and/or brain natriuretic peptide), *or* - combinations of the above Exclusions: - pregnancy - haemodynamic instability (defined as systolic blood pressure <90mmHg or a pressure drop of ≥40mmHg for >15 minutes if not caused by arrhythmia, hypovolaemia or sepsis) Subgroups: - age: ≤75 yrs / >75 yrs - type of thrombolytic agent

	Details
	- systemic vs. local (catheter-directed) administration - lower vs. standard dose thrombolysis (for example, as defined in the MOPPET trial (Sharifi 2013): ≥50kg = 10mg t-PA in 1 min followed by 40mg in 2 hrs; <50kg = 0.5mg/kg total dose: 10mg in 1 min followed by remainder in 2 hrs)
Intervention	Thrombolysis given in addition to standard accepted anticoagulation therapy for acute PE Thrombolytic agents may include: - tissue plasminogen activator t-PA: alteplase (Activase), reteplase (Retavase), tenecteplase (TNKase) - anistreplase (Eminase) - streptokinase (Kabikinase, Streptase) - urokinase (Abbokinase)
Comparator	Placebo given in addition to any standard accepted anticoagulation therapy for acute PE Any standard accepted anticoagulation therapy for acute PE alone
Outcomes	All-cause mortality Major bleeding Composite clinical outcome of death OR haemodynamic collapse/treatment escalation* VTE-related mortality VTE recurrence Quality of Life Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Length of hospital stay * where data are available, a sensitivity analysis will be undertaken to include then exclude patients given rescue thrombolysis
Other criteria for inclusion / exclusion of studies	**Exclusion** Randomised controlled trials that: - only compare different dosages of same thrombolytic drug - only compare different types of thrombolytic drug - compare thrombolysis with surgical thrombectomy or with combined pharmacomechanical methods of removing or dissolving a blood clot Non-randomised controlled studies Prospective comparative observational studies Retrospective comparative observational studies Narrative reviews, non-comparative studies, case series, case reports
Search strategies	See Appendix D:
Review strategies	○ A list of excluded studies will be provided following sifting of the database ○ Data on all included studies will be extracted into evidence tables ○ Where statistically possible, a meta-analytical approach will be used to give an overall summary effect

	Details
	○ All critical and important outcomes from evidence will be presented in GRADE profiles or modified profiles (where appropriate) and further summarised in evidence statements

C.2 Review question 2: Compression stockings for PTS prevention

	Details
Review Question	What is the effectiveness of stockings to prevent post-thrombotic syndrome (PTS) in people with confirmed proximal DVT?
Objectives	The review aims to establish the clinical and cost-effectiveness of long-term wear of stockings to prevent the development of PTS in patients who have had a confirmed proximal deep vein thrombosis (that is, a DVT of the popliteal vein or above).
Type of Review	Intervention
Language	English only
Study Design	Randomised controlled trials (RCTs), systematic reviews of RCTs Systematic reviews must have the same inclusion and exclusion criteria as defined in this protocol, and meet the quality standards defined in the NICE clinical guidelines methods handbook
Status	Published papers (full text only)
Population	Adults (18+) with confirmed proximal deep vein thrombosis (DVT) Exclusions: - patients with distal DVT only - patients with suspected DVT not confirmed by objective diagnostic method Subgroups: - length of stocking (below/above knee) - first episode vs. recurrent DVT - 3-6month anticoagulation vs. long-term anticoagulation therapy - duration of stocking wear
Intervention	Graduated compression hosiery (including stockings, tights and bandages) worn on the DVT affected leg
Comparator	No stocking Placebo stocking
Outcomes	Post-thrombotic syndrome (incidence and/or severity) Adherence

	Details
	Quality of life VTE recurrence VTE related mortality Adverse skin events
Other criteria for inclusion / exclusion of studies	**Exclusion** Studies where interventions support tights rather than graduated compression Non-randomised controlled studies Prospective comparative observational studies Retrospective comparative observational studies Narrative reviews, non-comparative studies, case series, case reports
Search strategies	See Appendix D:
Review strategies	○ A list of excluded studies will be provided following sifting of the database ○ Data on all included studies will be extracted into evidence tables ○ Where statistically possible, a meta-analytical approach will be used to give an overall summary effect ○ All critical and important outcomes from evidence will be presented in GRADE profiles or modified profiles (where appropriate) and further summarised in evidence statements

Appendix D: Search strategy

D.1 Review question 1: Thrombolysis for PE

D.1.1 Clinical search summary

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 7. The Medline search strategy is shown in Table 8. The same strategy was translated for the other databases listed.

Table 7: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Ovid, Wiley)	30/03/2015	8
Database of Abstracts of Reviews of Effects – DARE (CRD, Ovid, Wiley)	30/03/2015	23
HTA database (CRD, Ovid, Wiley)	30/03/2015	1
CENTRAL (Ovid, Wiley)	30/03/2015	268
MEDLINE (Ovid)	30/03/2015	1304
MEDLINE In-Process (Ovid)	30/03/2015	44
EMBASE (Ovid)	30/03/2015	1704

Table 8: Clinical search terms (Medline)

Line number/Search term/Number retrieved
1 exp Pulmonary Embolism/ (31902)
2 ((pulmonary or lung) adj4 (embolism* or thromboembolism* or emboli or infarction)).tw. (29256)
3 1 or 2 (42049)
4 Ventricular Dysfunction, Right/ (3821)
5 ("ventricular* dysfunction*" adj4 right*).tw. (1541)
6 ("ventricular* failure*" adj4 right*).tw. (1551)
7 (rv adj4 (dysfunction* or failure*)).tw. (1277)
8 or/4-7 (6362)
9 3 or 8 (47610)
10 Thrombolytic Therapy/ (18755)
11 Fibrinolytic Agents/ (24117)
12 ((fibrinolytic or thrombolytic or antithrombotic or antithrombic or thrombolysis* or thrombolyses*) adj4 (drug* or agent* or therap*)).tw. (20212)
13 (thrombolysis or fibrolysis or fibrolytic*).tw. (17102)
14 Tissue Plasminogen Activator/ (15635)
15 ("tissue plasminogen activator" or t-pa).tw. (12286)
16 Urokinase-Type Plasminogen Activator/ or Streptokinase/ or Anistreplase/ (17659)
17 (alteplase or actilyse or activase or reteplase, or rapilysin or retavase or tenecteplase or metalyse or TNKase).tw. (1868)
18 (anistreploase or eminase or streptokinase or Kabikinase or streptase or urokinase or syner-kinase or synerkinase or ukidan or abbokinase).tw. (18571)
19 (lysatec* or plasminogen* or tisokinase* or ttpa or varidase* or streptodornase* or u-pa or renokinase* or anistreplase* or iminase* or anistreplase* or apsac*).tw. (36422)
20 or/10-19 (88951)
21 9 and 20 (4617)

Line number/Search term/Number retrieved	
22	animals/ not humans/ (3909440)
23	21 not 22 (4455)
24	limit 23 to english language (3146)
25	Meta-Analysis.pt. (53636)
26	Meta-Analysis as Topic/ (14038)
27	Review.pt. (1927672)
28	exp Review Literature as Topic/ (7876)
29	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (63515)
30	(review$ or overview$).ti. (275827)
31	(systematic$ adj5 (review$ or overview$)).tw. (58603)
32	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4489)
33	((studies or trial$) adj2 (review$ or overview$)).tw. (25463)
34	(integrat$ adj3 (research or review$ or literature)).tw. (5592)
35	(pool$ adj2 (analy$ or data)).tw. (14501)
36	(handsearch$ or (hand adj3 search$)).tw. (5417)
37	(manual$ adj3 search$).tw. (3202)
38	or/25-37 (2090832)
39	animals/ not humans/ (3909440)
40	38 not 39 (1955083)
41	Randomized Controlled Trial.pt. (387105)
42	Controlled Clinical Trial.pt. (88827)
43	Clinical Trial.pt. (490674)
44	exp Clinical Trials as Topic/ (285917)
45	Placebos/ (32662)
46	Random Allocation/ (82333)
47	Double-Blind Method/ (128228)
48	Single-Blind Method/ (20026)
49	Cross-Over Studies/ (35346)
50	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (753059)
51	(random$ adj3 allocat$).tw. (21180)
52	placebo$.tw. (154393)
53	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (125837)
54	(crossover$ or (cross adj over$)).tw. (57530)
55	or/41-54 (1405102)
56	animals/ not humans/ (3909440)
57	55 not 56 (1309494)
58	40 or 57 (3021761)
59	24 and 58 (1304)

D.1.2 Economic search summary

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 9. The search strategy is shown in Table 10. The same strategy was translated for the other databases listed.

Table 9: Economic search summary, review question 1

Databases	Version/files	No. retrieved
NHS EED (Ovid, Wiley)	Issue 1 of 4, January 2015	5

Databases	Version/files	No. retrieved
HTA database (CRD, Ovid, Wiley)	Issue 1 of 4, January 2015	1
MEDLINE (Ovid)	1946 to March Week 5 2015	204
MEDLINE In-Process (Ovid)	April 06, 2015	9
EMBASE (Ovid)	1980 to 2015 Week 14	396

Table 10: Economic search strategy, review question 1

Database: Medline
Database: Ovid MEDLINE(R) <1946 to March Week 5 2015> Search Strategy: --- 1 exp Pulmonary Embolism/ (31911) 2 ((pulmonary or lung) adj4 (embolism* or thromboembolism* or emboli or infarction)).tw. (29267) 3 1 or 2 (42064) 4 Ventricular Dysfunction, Right/ (3824) 5 ("ventricular* dysfunction*" adj4 right*).tw. (1544) 6 ("ventricular* failure*" adj4 right*).tw. (1552) 7 (rv adj4 (dysfunction* or failure*)).tw. (1279) 8 or/4-7 (6369) 9 3 or 8 (47631) 10 Thrombolytic Therapy/ (18758) 11 Fibrinolytic Agents/ (24126) 12 ((fibrinolytic or thrombolytic or antithrombotic or antithrombic or thrombolysis* or thrombolyses*) adj4 (drug* or agent* or therap*)).tw. (20220) 13 (thrombolysis or fibrolysis or fibrolytic*).tw. (17109) 14 Tissue Plasminogen Activator/ (15637) 15 ("tissue plasminogen activator" or t-pa).tw. (12289) 16 Urokinase-Type Plasminogen Activator/ or Streptokinase/ or Anistreplase/ (17659) 17 (alteplase or actilyse or activase or reteplase, or rapilysin or retavase or tenecteplase or metalyse or TNKase).tw. (1869) 18 (anistreploase or eminase or streptokinase or Kabikinase or streptase or urokinase or syner-kinase or synerkinase or ukidan or abbokinase).tw. (18574) 19 (lysatec* or plasminogen* or tisokinase* or ttpa or varidase* or streptodornase* or u-pa or renokinase* or anistreplase* or iminase* or anistreplase* or apsac*).tw. (36430) 20 or/10-19 (88978) 21 9 and 20 (4618) 22 animals/ not humans/ (3909986) 23 21 not 22 (4456) 24 limit 23 to english language (3146) 25 Economics/ (26583) 26 exp "Costs and Cost Analysis"/ (185787) 27 Economics, Dental/ (1858) 28 exp Economics, Hospital/ (20093) 29 exp Economics, Medical/ (13502) 30 Economics, Nursing/ (3913) 31 Economics, Pharmaceutical/ (2556) 32 Budgets/ (9909) 33 exp Models, Economic/ (10546)

Database: Medline

34 Markov Chains/ (10210)
35 Monte Carlo Method/ (20665)
36 Decision Trees/ (8997)
37 econom$.tw. (160287)
38 cba.tw. (8795)
39 cea.tw. (16458)
40 cua.tw. (800)
41 markov$.tw. (11932)
42 (monte adj carlo).tw. (21370)
43 (decision adj3 (tree$ or analys$)).tw. (8552)
44 (cost or costs or costing$ or costly or costed).tw. (314088)
45 (price$ or pricing$).tw. (23548)
46 budget$.tw. (17627)
47 expenditure$.tw. (35604)
48 (value adj3 (money or monetary)).tw. (1367)
49 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2877)
50 or/25-49 (667647)
51 "Quality of Life"/ (123322)
52 quality of life.tw. (142752)
53 "Value of Life"/ (5423)
54 Quality-Adjusted Life Years/ (7380)
55 quality adjusted life.tw. (6192)
56 (qaly$ or qald$ or qale$ or qtime$).tw. (5095)
57 disability adjusted life.tw. (1236)
58 daly$.tw. (1216)
59 Health Status Indicators/ (20288)
60 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15690)
61 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1004)
62 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2734)
63 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
64 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (333)
65 (euroqol or euro qol or eq5d or eq 5d).tw. (4090)
66 (qol or hql or hqol or hrqol).tw. (25546)
67 (hye or hyes).tw. (53)
68 health$ year$ equivalent$.tw. (38)
69 utilit$.tw. (114395)
70 (hui or hui1 or hui2 or hui3).tw. (871)
71 disutili$.tw. (216)
72 rosser.tw. (71)
73 quality of wellbeing.tw. (5)
74 quality of well-being.tw. (332)
75 qwb.tw. (172)
76 willingness to pay.tw. (2288)
77 standard gamble$.tw. (652)
78 time trade off.tw. (751)
79 time tradeoff.tw. (203)
80 tto.tw. (601)

Database: Medline
81 or/51-80 (327214)
82 50 or 81 (950363)
83 24 and 82 (204)

D.2 Review question 2: Compression stockings for PTS prevention

D.2.1 Clinical search summary

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 11. The Medline search strategy is shown in Table 12. The same strategy was translated for the other databases listed.

Table 11: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Ovid, Wiley)	30/03/2015	21
Database of Abstracts of Reviews of Effects – DARE (CRD, Ovid, Wiley)	30/03/2015	22
HTA database (CRD, Ovid, Wiley)	30/03/2015	9
CENTRAL (Ovid, Wiley)	30/03/2015	351
MEDLINE (Ovid)	30/03/2015	715
MEDLINE In-Process (Ovid)	30/03/2015	34
EMBASE (Ovid)	30/03/2015	587

Table 12: Clinical search terms (Medline)

Line number/Search term/Number retrieved
1 Thromboembolism/ or Thrombophlebitis/ or Venous Thrombosis/ or venous thromboembolism/ (61420)
2 ((venous or vein) adj (thrombos* or thrombus or thromboembolism)).tw. (42465)
3 (dvt or vte).tw. (10315)
4 (thrombophlebitis or phlebothrombos*).tw. (5227)
5 ((proximal or "above knee" or above-knee) adj4 (thrombos* or thrombus or thromboembolism)).tw. (1173)
6 or/1-5 (79766)
7 Postthrombotic Syndrome/ (288)
8 Postphlebitic Syndrome/ (554)
9 ((post-thrombotic or "post thrombotic" or postthrombotic or postphlebitic or post-phlebitic or "post phlebitic") adj1 syndrome*).tw. (1414)
10 (venous adj stasis adj syndrome*).tw. (29)
11 or/7-10 (1812)
12 6 or 11 (80335)
13 bandages/ or Compression Bandages/ or stockings, compression/ (15204)
14 (stocking* or hose or tights or bandage* or wrap*).tw. (16799)
15 13 or 14 (29391)
16 12 and 15 (1911)
17 animals/ not humans/ (3909440)

Line number/Search term/Number retrieved	
18	16 not 17 (1901)
19	limit 18 to english language (1419)
20	Meta-Analysis.pt. (53636)
21	Meta-Analysis as Topic/ (14038)
22	Review.pt. (1927672)
23	exp Review Literature as Topic/ (7876)
24	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (63515)
25	(review$ or overview$).ti. (275827)
26	(systematic$ adj5 (review$ or overview$)).tw. (58603)
27	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (4489)
28	((studies or trial$) adj2 (review$ or overview$)).tw. (25463)
29	(integrat$ adj3 (research or review$ or literature)).tw. (5592)
30	(pool$ adj2 (analy$ or data)).tw. (14501)
31	(handsearch$ or (hand adj3 search$)).tw. (5417)
32	(manual$ adj3 search$).tw. (3202)
33	or/20-32 (2090832)
34	animals/ not humans/ (3909440)
35	33 not 34 (1955083)
36	Randomized Controlled Trial.pt. (387105)
37	Controlled Clinical Trial.pt. (88827)
38	Clinical Trial.pt. (490674)
39	exp Clinical Trials as Topic/ (285917)
40	Placebos/ (32662)
41	Random Allocation/ (82333)
42	Double-Blind Method/ (128228)
43	Single-Blind Method/ (20026)
44	Cross-Over Studies/ (35346)
45	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (753059)
46	(random$ adj3 allocat$).tw. (21180)
47	placebo$.tw. (154393)
48	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (125837)
49	(crossover$ or (cross adj over$)).tw. (57530)
50	or/36-49 (1405102)
51	animals/ not humans/ (3909440)
52	50 not 51 (1309494)
53	35 or 52 (3021761)
54	19 and 53 (715)

D.2.2 Economic search summary

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 13. The search strategy is shown in Table 14. The same strategy was translated for the other databases listed.

Table 13: Economic search summary, review question 2

Databases	Version/files	No. retrieved
NHS EED (Ovid, Wiley)	Issue 1 of 4, January 2015	6
HTA database (Ovid, Wiley)	Issue 1 of 4, January 2015	9

Databases	Version/files	No. retrieved
MEDLINE (Ovid)	1946 to March Week 5 2015	168
MEDLINE In-Process (Ovid)	April 06, 2015	19
EMBASE (Ovid)	1980 to 2015 Week 14	281

Table 14: Economic search strategy, review question 2

Database: Medline
Database: Ovid MEDLINE(R) <1946 to March Week 5 2015> Search Strategy: --- 1 Thromboembolism/ or Thrombophlebitis/ or Venous Thrombosis/ or venous thromboembolism/ (61448) 2 ((venous or vein) adj (thrombos* or thrombus or thromboembolism)).tw. (42493) 3 (dvt or vte).tw. (10324) 4 (thrombophlebitis or phlebothrombos*).tw. (5230) 5 ((proximal or "above knee" or above-knee) adj4 (thrombos* or thrombus or thromboembolism)).tw. (1174) 6 or/1-5 (79808) 7 Postthrombotic Syndrome/ (288) 8 Postphlebitic Syndrome/ (554) 9 ((post-thrombotic or "post thrombotic" or postthrombotic or postphlebitic or post-phlebitic or "post phlebitic") adj1 syndrome*).tw. (1414) 10 (venous adj stasis adj syndrome*).tw. (29) 11 or/7-10 (1812) 12 6 or 11 (80377) 13 bandages/ or Compression Bandages/ or stockings, compression/ (15209) 14 (stocking* or hose or tights or bandage* or wrap*).tw. (16802) 15 13 or 14 (29399) 16 12 and 15 (1911) 17 animals/ not humans/ (3909986) 18 16 not 17 (1901) 19 limit 18 to english language (1419) 20 Economics/ (26583) 21 exp "Costs and Cost Analysis"/ (185787) 22 Economics, Dental/ (1858) 23 exp Economics, Hospital/ (20093) 24 exp Economics, Medical/ (13502) 25 Economics, Nursing/ (3913) 26 Economics, Pharmaceutical/ (2556) 27 Budgets/ (9909) 28 exp Models, Economic/ (10546) 29 Markov Chains/ (10210) 30 Monte Carlo Method/ (20665) 31 Decision Trees/ (8997) 32 econom$.tw. (160287) 33 cba.tw. (8795) 34 cea.tw. (16458) 35 cua.tw. (800) 36 markov$.tw. (11932) 37 (monte adj carlo).tw. (21370) 38 (decision adj3 (tree$ or analys$)).tw. (8552)

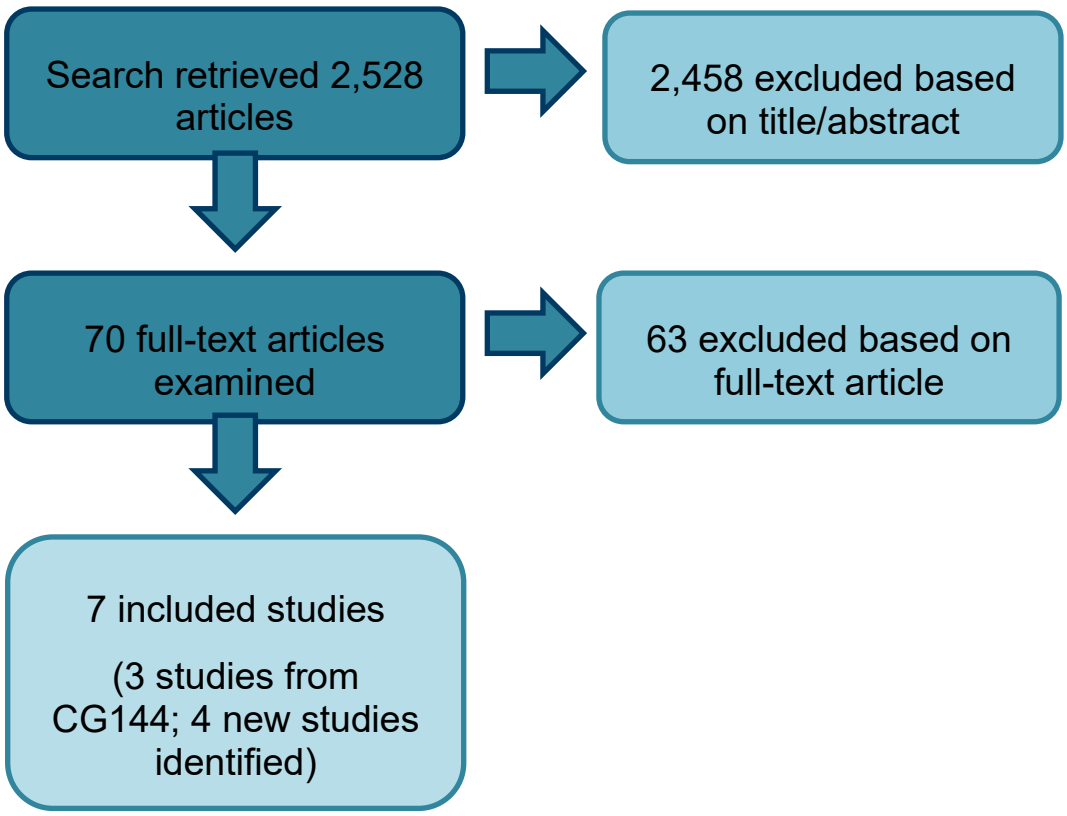
Database: Medline

39 (cost or costs or costing$ or costly or costed).tw. (314088)
40 (price$ or pricing$).tw. (23548)
41 budget$.tw. (17627)
42 expenditure$.tw. (35604)
43 (value adj3 (money or monetary)).tw. (1367)
44 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2877)
45 or/20-44 (667647)
46 "Quality of Life"/ (123322)
47 quality of life.tw. (142752)
48 "Value of Life"/ (5423)
49 Quality-Adjusted Life Years/ (7380)
50 quality adjusted life.tw. (6192)
51 (qaly$ or qald$ or qale$ or qtime$).tw. (5095)
52 disability adjusted life.tw. (1236)
53 daly$.tw. (1216)
54 Health Status Indicators/ (20288)
55 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15690)
56 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1004)
57 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2734)
58 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
59 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (333)
60 (euroqol or euro qol or eq5d or eq 5d).tw. (4090)
61 (qol or hql or hqol or hrqol).tw. (25546)
62 (hye or hyes).tw. (53)
63 health$ year$ equivalent$.tw. (38)
64 utilit$.tw. (114395)
65 (hui or hui1 or hui2 or hui3).tw. (871)
66 disutili$.tw. (216)
67 rosser.tw. (71)
68 quality of wellbeing.tw. (5)
69 quality of well-being.tw. (332)
70 qwb.tw. (172)
71 willingness to pay.tw. (2288)
72 standard gamble$.tw. (652)
73 time trade off.tw. (751)
74 time tradeoff.tw. (203)
75 tto.tw. (601)
76 or/46-75 (327214)
77 45 or 76 (950363)
78 19 and 77 (168)

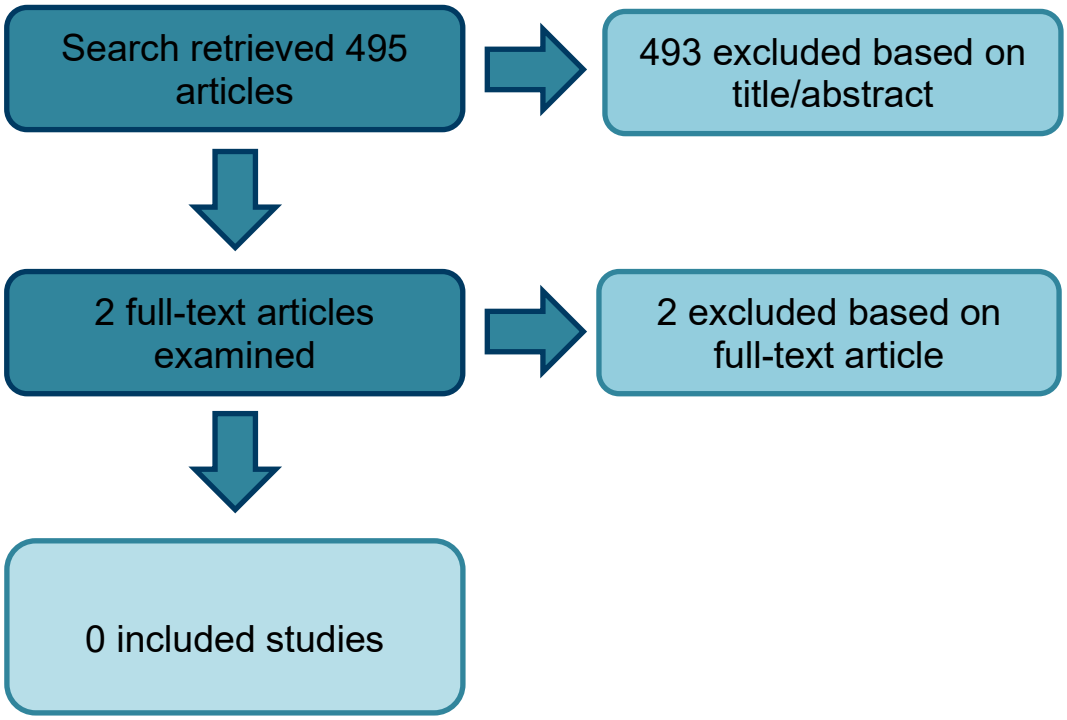
Appendix E: Review flowcharts

E.1 Review question 1: Thrombolysis for PE

E.1.1 Clinical review flowchart

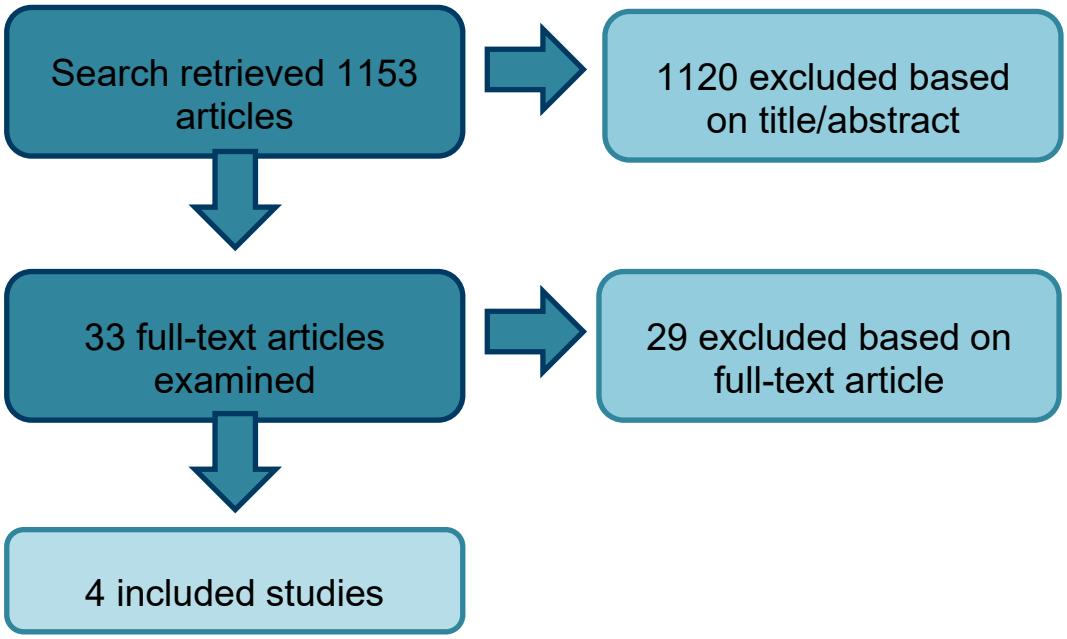


E.1.2 Economic review flowchart

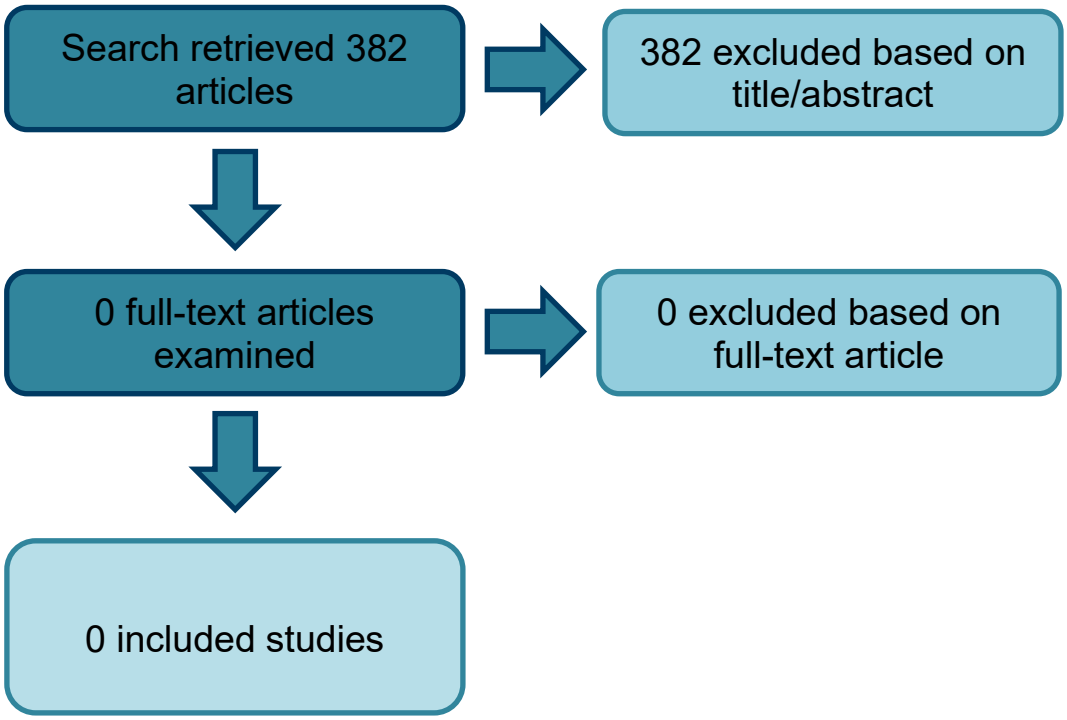


E.2 Review question 2: Compression stockings for PTS prevention

E.2.1 Clinical review flowchart



E.2.2 Economic review flowchart



Appendix F:Excluded studies

F.1 Review question 1: Thrombolysis for PE

F.1.1 Clinical excluded studies table

Reference	Reason for exclusion
Abedelsamad A, El-Morsi A, Mansour A. (2011) Efficacy and safety of high dose versus low dose streptokinase for treatment of submassive pulmonary embolism. The Egyptian Heart Journal 63: 67-72.	Non-randomised comparison of two different dosages of same thrombolytic.
Agnelli G, Iorio A, Parise P, Goldhaber S, Levine M. (1997) Fibrinogenolysis and thrombin generation after reduced dose bolus or conventional rt-PA for pulmonary embolism. The Coagulation Project Investigators of the Bolus Alteplase Pulmonary Embolism Group. Blood, Coagulation & Fibrinolysis 8: 216-222.	Comparator does not meet protocol (no 'standard anticoagulation' treatment arm).
Agnelli G, Becattini C, Kirschstein T. (2002) Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. Archives of Internal Medicine 162: 2537-2541.	Systematic review did not meet protocol: data for a normotensive PE subgroup with RVD not specifically reported. Used for cross-checking. No additional relevant studies identified.
Anderson D, Levine M. (1992) Thrombolytic therapy for the treatment of acute pulmonary embolism. Canadian Medical Association Journal 146: 1317-1324.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Anon. (2002) Early lytic treatment of massive pulmonary embolism. Cardiovascular Journal of South Africa 13: 218-219.	Incorrect publication type (editorial).
Anon. (1970) Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA 214: 2163-2172.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Avgerinos E, Chaer R. (2015) Catheter-directed interventions for acute pulmonary embolism. Journal of Vascular Surgery 61: 559-565.	Non-systematic review.
Arnesen B, Eie H, Hol R. (1978) A prospective study of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Medica Scandinavica 203: 457-463.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Capstick T, Henry M. (2005) Efficacy of thrombolytic agents in the treatment of pulmonary embolism. European Respiratory Journal 26: 864-874.	Systematic review – includes study populations and comparators that do not meet protocol. Used for cross-checking. No additional relevant studies identified.

Reference	Reason for exclusion
Charbonnier B. (1984). Multicentre trial of two urokinase protocols in severe pulmonary embolism. Arch Mal Coeur 7: 773-781.	Not in English.
Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky R., et al. (2014) Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 311: 2414-2421.	Systematic review did not meet protocol: includes interventions not covered by the update remit (ultrasound-assisted catheter-directed thrombolysis). Used for cross-checking. No additional relevant studies identified.
Chavatzas D. (1975) A study of streptokinase therapy in acute pulmonary embolism. The Journal of Cardiovascular Surgery 16: 404-408.	Not an RCT.
Chen H, Ren C, Chen H. (2014) Thrombolysis Versus Anticoagulation for the Initial Treatment of Moderate Pulmonary Embolism: A Meta-Analysis of Randomized Controlled Trials. Respiratory Care 59: 1880-1887.	Systematic review did not meet protocol: included 7 studies not in English; data for a normotensive PE subgroup with RVD not specifically reported. Used for cross-checking. No additional relevant studies identified.
Dalla-Volta S, Palla A, Santolicandro A, Giuntini C, Pengo V., et al. (1992) PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. Journal of the American College of Cardiology 20: 520-526.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Daniels L, Parker J, Patel S, Grodstein F, Goldhaber S. (1997) Relation of duration of symptoms with response to thrombolytic therapy in pulmonary embolism. The American Journal of Cardiology 80: 184-188	Not an RCT.
Diehl J, Meyer G, Igual J, Collignon M, Giselbrecht M., et al. (1992) Effectiveness and safety of bolus administration of alteplase in massive pulmonary embolism. The American Journal of Cardiology 70: 1477-1480.	Not an RCT.
Dong B, Hao Q, Yue J,Wu T, Liu G. (2009) Thrombolytic therapy for pulmonary embolism. The Cochrane Database of Systematic Reviews. Issue 3: CD004437	Systematic review did not meet protocol: data for a normotensive PE subgroup with RVD not specifically reported. Used for cross-checking. No additional relevant studies identified.
Dotter C, Seaman A, Rosch J, Porter J. (1979) Streptokinase and heparin in the treatment of major pulmonary embolism: a randomised comparison. Vascular Surgery 13: 42-52.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.

Reference	Reason for exclusion
Erkan L, Findik S, Atici A, Uzun O. (2002) Thrombolytic therapy in massive pulmonary thromboembolism. European Respiratory Journal 20: 237s	Incorrect publication type (conference abstract); study comparator does not meet protocol (no 'standard anticoagulation' treatment arm).
Francois G, Charbonnier B, Raynaud P. (1986) Treatment of acute pulmonary embolism by urokinase compared with the association plasminogen-urokinase: Results in 67 cases. Arch Mal Coeur 79: 435-442	Not in English.
Giuntini C, Marini C, Di Ricco G, Palla R, Giacomelli V, Rindi M. (1984) A controlled clinical trial on the effect of heparin infusion and two regimens of urokinase in acute pulmonary embolism. Giornale Italiano di Cardiologi 14: Suppl1: 26-29	Study population and outcomes do not meet protocol.
Goldhaber S, Kessler C, Heit J, Markis J, Sharma G., et al. (1988) Randomised controlled trial of recombinant plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. Lancet 2: 293-298	Comparator does not meet protocol (no 'standard anticoagulation' treatment arm).
Goldhaber S, Kessler C, Heit J, Elliott C, Friedenberg W., et al. (1992) Recombinant tissue-type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: a randomized controlled multicenter trial. Journal of the American College of Cardiology 20: 24-30	Comparator does not meet protocol (no 'standard anticoagulation' treatment arm).
Goldhaber S, Agnelli G, Levine M. (1994) Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. Chest 106: 718-724.	Comparator does not meet protocol (no 'standard anticoagulation' treatment arm).
Haire W. (2003) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. Current Hematology Reports. 2: 405-406	Incorrect publication type: report of included study (Konstantinides, 2002).
Harris T, Meek S. (2005) When should we thrombolyse patients with pulmonary embolism? A systematic review of the literature. Emergency Medicine Journal 22: 766-771.	Non-systematic review.
Hyers T, Stengle J, Sherry S. (1970) Treatment of pulmonary embolism with urokinase. Results of clinical trial (phase 1). Circulation 42: 979-980.	Incorrect publication type (editorial).
Jerjes-Sanchez C, Ramirez-Rivera A, Arriaga-Nava R, Iglesias-Gonzalez S, Gutierrez P., et al. (2001) High dose and short-term streptokinase infusion in patients with pulmonary embolism: prospective with seven-year follow-up trial. Journal of Thrombosis and Thrombolysis 12: 237-247.	Not an RCT.
Jerjes-Sanchez C, Ramirez-Rivera A, Lourdes G, Arriaga-Nava R, Valencia S., et al. (1995) Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial. Journal of Thrombosis and Thrombolysis 2: 227-229.	Study population does not meet protocol.

Reference	Reason for exclusion
Jerjes-Sanchez C, Villarreal-Umana S, Ramirez-Rivera A, Garcia-Sosa A, Miguel-Canseco L., et al. (2009) Improving adjunctive treatment in pulmonary embolism and fibrinolytic therapy. The role of enoxaparin and weight-adjusted unfractionated heparin. Journal of Thrombosis and Thrombolysis 27: 154-162.	Not an RCT.
Kline J, Kabrhel C, Courtney M, Diercks D, Jones A., et al. (2013) Quality of life outcomes in a randomized trial of tenecteplase versus placebo for submassive pulmonary embolism. Journal of Thrombosis and Haemostasis 11: 406.	Conference abstract for included study (Kline, 2014).
Kline J, Hernandez,J, Hogg M, Jones A, Courtney D., et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism the includes quality of life outcomes. Emergency Medicine Australiasia 25: 515-526.	Incorrect publication type: outlines study design and methodology for included study (Kline 2014). Used for supplementary detail.
Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W. (1998) Comparison of alteplase versus heparin for resolution of major pulmonary embolism. American Journal of Cardiology 82: 966-970.	Not an RCT.
Konstantinides S. (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. American Heart Journal 163: 1-33.	Incorrect publication type: research protocol for included study (Meyer et al. 2014). Used for supplementary detail.
Kucher N, Boekstegers P, Muller O, Kupatt C, Beyer-Westendorf J., et al. (2014) Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 129: 479-486.	Intervention does not meet review protocol (ultrasound-assisted catheter-directed thrombolysis).
Kuo W, Gould M, Louie J, Rosenberg J, Sze D, Hofmann L. (2009) Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. Journal of Vascular and Interventional Radiology 20: 1431-1440.	Systematic review of non-RCTs; study population does not meet protocol.
Levine M, Hirsh J, Weitz J, Cruickshank M, Neemeh J, Turpie A, Gent M. (1990) A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 98: 1473-1479.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Liu Y, Lu Y, Song J, Li D, Liu H, Yang J. (2014) Recombinant tissue plasminogen activator for hemodynamically stable patients experiencing an acute pulmonary embolism: a meta-analysis. Thrombosis research 134: 50-56.	Systematic review did not meet protocol: includes study populations with no objective evidence of RVD. Used for cross-checking. No additional relevant studies identified.
Ly B, Arnesen H, Eie H, Hol R. (1978) A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Medica Scandinavica 203: 465-470.	Same study as Arnesen (1978).

Reference	Reason for exclusion
Marini C, Di Ricco G, Rossi G, Rindi M, Palla R, Giuntini C. (1988) Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: a randomized clinical trial. Respiration: International Review of Thoracic Diseases 54: 162-173	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Marti C, John G, Konstantinides S, Combescure C, Sanchez O., et al. (2015) Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. European Heart Journal 36: 605-614.	Systematic review did not meet protocol: includes study populations with no objective evidence of RVD. Used for cross-checking. No additional relevant studies identified.
Meneveau N, Schiele F, Metz D, Valette B, Attali P., et al. (1998) Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. Journal of the American College of Cardiology 31: 1057-1063	Study population and comparator do not meet protocol.
Meneveau N, Schiele F, Vuillemenot A, Valette B, Grollier G., et al. (1997) Streptokinase vs alteplase in massive pulmonary embolism. A randomized trial assessing right heart haemodynamics and pulmonary vascular obstruction. European Heart Journal 18: 1141-1148	Study population and comparator do not meet protocol.
Meyer G, Sors H, Charbonnier B, Kasper W, Bassand J., et al. (1992) Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. The European Cooperative Study Group for Pulmonary Embolism. Journal of the American College of Cardiology 19: 239-245.	Study population and comparator do not meet protocol.
Nakamura S, Takano H, Kubota Y, Asai K, Shimizu W. (2014) Impact of the efficacy of thrombolytic therapy on the mortality of patients with acute submassive pulmonary embolism: a meta-analysis. Journal of Thrombosis and Haemostasis 12: 1086-1095.	Systematic review did not meet protocol: does not include all relevant outcomes. Used for cross-checking. No additional relevant studies identified.
Perlroth D, Sanders G, Gould M. (2007) Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Archives of Internal Medicine 167: 74-80.	Cost-effectiveness study.
Ramakrishnan N. (2007) Thrombolysis is not warranted in submassive pulmonary embolism: a systematic review and meta-analysis. Critical Care and Resuscitation 4: 357-363.	Systematic review did not meet protocol: includes study populations with no objective evidence of RVD. Used for cross-checking. No additional relevant studies identified.
Riera-Mestre A, Becattini C, Giustozzi M, Agnelli G. (2014) Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. Thrombosis Research 134: 1265-1271.	Systematic review did not meet protocol: includes study populations with no objective evidence of RVD. Used for cross-checking. No additional relevant studies identified.

Reference	Reason for exclusion
Sasahara A, Hyers T, Cole C, Ederer F, Murray J, Wenger N. (1973) The urokinase pulmonary embolism trial: A national cooperative study. Circulation 47: Supplement II: 1-108.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Sasahara A, Henkin J, Janicki R. (1988) Urokinase versus tissue plasminogen activator in pulmonary embolism. Lancet 2 (8612): 691-692.	Incorrect publication type (letter).
Sors H, Pacouret G, Azarian R, Meyer G, Charbonnier B, Simonneau G. (1994) Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. Chest 106: 712-717.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Stein P, Alavi A, Athanasoulis C, Coleman R, Froelich J., et al. (1990) Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. Chest 97: 528-533.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
Tebbe U, Graf A, Kamke W, Zahn R, Forycki F, Kratzsch G, Berg G. (1999) Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. American Heart Journal 138: 39-44.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Tebbe U, Bramlage P, Graf A, Lechleitner P, Bode C., et al. (2009) Desmoteplase in acute massive pulmonary thromboembolism. Thrombosis and Haemostasis 101: 557-562.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Thabut G, Thabut D, Myers R, Bernard-Chabert B, Marrash-Chahla R., et al. (2002) Thrombolytic therapy of pulmonary embolism: a meta-analysis. Journal of the American College of Cardiology 40: 1660-1667.	Systematic review did not meet protocol: data for a normotensive PE subgroup with RVD not specifically reported. Used for cross-checking. No additional relevant studies identified.
Tibbutt D, Davies J, Anderson J, Fletcher E, Hamill J., et al. (1974) Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonay embolism. BMJ 1: 543-547.	Study population does not meet protocol. Data for a normotensive PE subgroup with RVD not specifically reported.
The UKEP Study Research Group. (1987) The UKEP study: multicentre clinical trial on two local regimens of urokinase in massive pulmonary embolism. European Heart Journal 8: 2-10.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Verstraete M, Miller G, Bounameaux H, Charbonnier B, Colle J., et al. (1988) Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 77: 353-360.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Walsh P, Stengle J, Sherry S.(1969) The urokinase-pulmonary embolism trial. Circulation 39: 153-156.	Incorrect publication type (editorial).
Wan S, Quinlan D, Agnelli G, Eikelboom J. (2004) Thrombolysis compared with heparin for the initial treatment of pulmonary	Systematic review did not meet protocol: data for a normotensive PE subgroup

Reference	Reason for exclusion
embolism: a meta-analysis of the randomized controlled trials. Circulation 110: 744-749.	with RVD not specifically reported. Used for cross-checking. No additional relevant studies identified.
Wang C, Zhai Z, Yang Y, Wu Q, Cheng Z., et al. (2010) Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter controlled trial. Chest 137: 254-262.	Comparator does not meet review protocol (no 'standard anticoagulation' treatment arm).
Worster A, Smith C, Silver S, Brown M. (2007) Thrombolytic Therapy for Submassive Pulmonary Embolism? Annals of Emergency Medicine 50: 78-84.	Systematic review - includes 2 trials both included in this review. Used for cross-checking.
Yang,Y.W. (2011) Efficacy and safety of two-hour regimen of recombinant streptokinase versus urokinase in massive and submassive pulmonary embolism: A randomized controlled trial. Respirology 16: 309.	Incorrect publication type (conference abstract); study comparator does not meet review protocol.

F.1.2 Economic excluded studies table

Reference	Reason for exclusion
Perlroth DJ, Sanders GD, Gould MK (2007) Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Archives of internal medicine 167: 74-80	Not applicable. More clinical evidence has transpired since this study was conducted. 5 of the 7 studies included in the present clinical review were published since this economic study.
Zamanian RT, Gould MK (2008) Effectiveness and cost effectiveness of thrombolysis in patients with acute pulmonary embolism. Current opinion in pulmonary medicine 14: 422-6	Narrative review only

F.2 Review question 2: Compression stockings for PTS prevention

F.2.1 Clinical excluded studies table

Reference	Reason for exclusion
Amsler F, Blattler W (2008) Compression therapy for occupational leg symptoms and chronic venous disorders – a meta-analysis of randomised controlled trials. Eur J Endovasc Surg 35:366-372	Not relevant population
Brandjes DPM, Rutten GCFM, Heijboer H, et al. (1989) Elastic compression stockings in the prevention of the post thrombotic syndrome in patients with a proximal deep vein thrombosis; an interim analysis. Thrombosis and Haemostasis 62:130	Abstract
Cate-Hoek AJ, Joore M, Hamulyak K, et al. (2011) Individually tailored elastic compression therapy and post thrombotic syndrome, a randomised multicentre trial (ideal DVT study). Journal of Thrombosis and Haemostasis 9(suppl 2):655	Abstract

Reference	Reason for exclusion
Cohen JM, Akl EA, Kahn SR (2012) Pharmacologic and compression therapies for postthrombotic syndrome. Chest 141:308-320	Treatment of PTS (systematic review, references checked)
Elton G (2004) Review: elastic compression stockings prevent post-thrombotic syndrome in patients with deep vein thrombosis. Evidence Based Nursing 7:86	Commentary
Galanaud J-P, Kahn SR (2013) The post-thrombotic syndrome: a 2012 therapeutic update. Current Treatment Options in Cardiovascular Medicine 15:153-163	Review/background
Galanaud J-P, Kahn SR (2014) Post-thrombotic syndrome: a 2014 update. Curr Opin Cardiol 29:514-519	Review/background (references checked)
Ginsberg JS, Hirsh J, Julian J, et al. (2001) Prevention and treatment of postphlebitic syndrome. Arch Intern Med 161:2105-2109	Prevention group not in RCT studies
Holmes CE, Bambace N, Lewis P, et al. (2014) Efficacy of a short source of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome. 19:42-48	Treatment of PTS
Kahn SR, Shbaklo H, Shapiro S, et al. (2007) Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX trial and Bio-SOX biomarker substudy): a randomised controlled trial. BMC Cardiovascular Disorders 7:21	Study protocol for SOX trial
Kahn SR, Shapiro S, Ducruet T, et al. (2014) Graduated compression stockings to treat acute leg pain associated with proximal DVT. Thromb Haemost 112:1137-1141	Not relevant outcomes
Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, et al. (2006) Review on the value of graduated elastic compression stockings after deep vein thrombosis. Thromb Haemost 96:441-445	Review (references checked)
Kanaan AO, Lepage JE, Djazayeri S, et al. (2012) Evaluating the role of compression stockings in preventing post-thrombotic syndrome: a review of the literature. Thrombosis 694851	Review (references checked)
Kolbach DN, Sandbrink MWC, Hamulyak K, et al. (2008) Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane Database of Systematic Reviews	References checked, 2 studies previously included in CG144, 2 studies not relevant
Musani MH, Matta F, Yaekoub AY, et al. (2010) Venous compression for prevention of postthrombotic syndrome: a meta-analysis. The American Journal of Medicine 123:735-740	Limited detail on methods (references checked)
Rutten GCFM, Brandjes DPM, Huisman N, et al. (1990) The effect of a size to fit graded compression stocking on the development of the post thrombotic syndrome (PTS) in patients with a proximal deep vein thrombosis, measured with a clinical score: an interim analysis. British Journal of Haematology 76(suppl 1):19	Abstract

Reference	Reason for exclusion
Schwahn-Schreiber C, Marshall M, Wienert V, et al. (2014) Wearing compression stockings after deep venous thrombosis of the leg is still advisable. Phlebologie 43:144-147	Commentary on the Kahn (2014) study
Strijkers RHW, ten Cate-Hoek AJ, Bukkems SFFW, et al. (2011) Management of deep vein thrombosis and prevention of post-thrombotic syndrome. BMJ 343:949-953	Review
Vedantham S, Goldhaber SZ, Kahm SR, et al. (2013) Rationale and design of the ATTRACT study – a multicentre randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with proximal deep vein thrombosis. Am Heart J 165:523-530	Study protocol, intervention not relevant
White R, Brown A, Lattimer CR, et al. (2013) Compression therapy post-deep vein thrombosis: how to best avoid post-thrombotic syndrome. Wounds UK 9:8-14	Review

Appendix G: Evidence tables

G.1 Review question 1: Thrombolysis for PE

G.1.1 Clinical evidence tables

Bibliographic reference	**Goldhaber S., et al. (1993) Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right ventricular function and pulmonary perfusion.**
Study type	RCT Multi-centre randomised trial using permuted block random number sequences; allocation concealment maintained (sealed envelopes), open-label study
Aim	To determine whether thrombolysis followed by anticoagulation is superior to anticoagulation alone in reversing echocardiographic evidence of RVD in PE; whether it improves pulmonary tissue perfusion more rapidly than anticoagulation alone, and whether it lowers incidence of recurrent PE.
Patient characteristics	Recruitment: November 1988 to July 1991 <u>Inclusion criteria:</u> - ≥18 years - Signs & symptoms of PE, confirmed by pulmonary angiogram or high probability ventilation perfusion scan - Onset of symptoms ≤14 days - Able to undergo baseline echocardiogram <u>Exclusion criteria:</u> - Major internal bleeding in past 6 months - Intracranial / intraspinal disease - Operation / biopsy in preceding 10 days - Occult blood in stool - Haematocrit <28% or platelet count <100,000/μL - BP> 200mm Hg systolic or 110 mm Hg diastolic

<table>
<tr><td>Bibliographic reference</td><td>Goldhaber S., et al. (1993) Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right ventricular function and pulmonary perfusion.</td></tr>
<tr><td></td><td>- Severe haptic function impairment
- Pregnancy
- Active infective endocarditis, haemorrhagic retinopathy
- End-stage conditions

<table><tr><th>Baseline demographic characteristics:</th><th>Intervention (n=46)</th><th>Control (n=55)</th></tr><tr><td>Male - n (%)</td><td>16 (35%)</td><td>28 (51%)</td></tr><tr><td>Age (mean, SD)</td><td>58 (17)</td><td>59 (17)</td></tr></table>
No significant differences between treatment groups on any baseline demographic or clinical characteristics

Note: baseline data reported correspond to full sample of 101 patients who were randomised, not the sub-sample of 46 patients with RVD at baseline for whom outcome data are extracted here.</td></tr>
<tr><td>Number of Patients</td><td>Randomised n=101 (Intervention: n=46, Control n=55)

Note: data are extracted only for 46 patients who had impaired RV wall movement (indicative of RVD) on echocardiogram at baseline (Intervention n=23, Control n=23). RVD is not confirmed in other patients.</td></tr>
<tr><td>Intervention</td><td>rt-PA (alteplase) + heparin (UFH)

Thrombolysis: 100mg rt-PA administered via IV infusion over 2 hours (50mg/hour). Administered prior to heparin.

Anticoagulation: UFH 1,000 units/hour IV when the partial thromboplastin time (PTT) was less than twice control; subsequently infused continuously to achieve a target PTT of 1.5-2.5 times the upper limit of normal.

Patients received heparin for at least 5 days, then oral anticoagulants to INR 2.0 – 4.0.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Goldhaber S., et al. (1993) Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right ventricular function and pulmonary perfusion.</td></tr>
<tr><td>Comparison</td><td>Heparin (UFH) only

UFH administered as 5,000 unit bolus followed by 1,000 units/hour IV infusion; subsequent doses administered to achieve a target PTT of 1.5-2.5 times the upper limit of normal.

Patients received heparin for at least 5 days, then oral anticoagulants to INR 2.0 – 4.0.</td></tr>
<tr><td>Length of follow up</td><td>14 days / while in hospital (up to 21 days for recurrent PE)</td></tr>
<tr><td>Location</td><td>USA – multicentre (number of participating hospitals not specified)</td></tr>
<tr><td>Outcomes measures and effect size</td><td><u>Clinical outcomes:</u>

- Change in RV function at 3 hrs and 24 hrs assessed qualitatively and quantitatively via echocardiogram (outcome not in review protocol)
- Lung perfusion at 24 hours assessed via lung perfusion scan (outcome not in review protocol)
- Mortality within 14 days (or while in hospital, if longer)
- PE recurrence within 14 days (or while in hospital, if longer)
- Major bleeding (requiring surgery, or any intracranial bleed) within 72 hours
- Reduction in haematocrit of >0.1 within 72 hours

<table>
<tr><th>Within 14 days:</th><th>Intervention (n=23)</th><th>Control (n=23)</th></tr>
<tr><td>Recurrent PE
- Fatal
- Non-fatal</td><td>0
0
0</td><td>5 (21.7%)
2 (8.7%)
3 (13.0%)</td></tr>
<tr><td>Major bleeding (meeting review protocol)</td><td colspan="2">Bleeding recorded for 3 intervention and 1 control patients, but not clear if these were among the n=46 with confirmed RVD at baseline. Data not used in analyses.</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Goldhaber S., et al. (1993) Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right ventricular function and pulmonary perfusion.**
	Notes: No other mortality than that recorded above (i.e. 2 incidences of fatal PE recurrence) One control patient who had a fatal PE was inappropriately enrolled. The patient was given secondary thrombolysis off protocol for a suspected recurrent PE but should have been excluded from enrolment altogether having sustained an undiagnosed head injury that led to intracranial bleeding prior to recruitment
Source of funding	Part funded by grant from Genentech, Inc who manufacture Activase (alteplase).
Comments	- Patients and clinicians not blinded to treatment, only those assessing echocardiograms were blinded to treatment allocation; - Data extracted for analyses correspond only to a subgroup of the study population who had confirmed RVD (n=46) – post-hoc subgroup analyses should be treated with caution

Bibliographic reference	**Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.**
Study type	RCT (double-blind, placebo-controlled) Randomisation according to a standard randomisation programme on 1:1 basis, fixed block size of n=6 at each centre; allocation concealment maintained.
Aim	To compare the effects of treatment with heparin plus alteplase with the effects of heparin plus placebo on the outcome of patients with acute submassive PE
Patient characteristics	September 1997 to August 2001 Inclusion criteria: Acute submassive PE with one of the following: - echocardiographically detected RVD, or - echocardiographically detected pulmonary-artery hypertension followed by confirmation of PE, or

<table>
<tr><th>Bibliographic reference</th><th>Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.</th></tr>
<tr><td></td><td>
- diagnosis of precapillary pulmonary hypertension based on catherisation of the right side of the heart followed by confirmation of PE

<u>Exclusion criteria:</u>
- >80years
- Haemodynamic instability (BP ≤90 mm Hg) with or without signs of cardiogenic shock
- Onset of symptoms >96hours before diagnosis
- Thrombolytic treatment, major surgery or biopsy in preceding 7days
- Major trauma preceding 10days
- Stroke, TIA, craniocerebral trauma or neurologic surgery in preceding 6months; GI bleeding in preceding 3months
- Uncontrolled hypertension, bleeding disorder, inability to tolerate alteplase, diabetic retinopathy, current anticoagulant therapy
- Pregnancy or lactation
- Life expectancy <6months
- Planned use of thrombolytic agents for extensive DVT

<table>
<tr><th>Baseline demographic characteristics:</th><th>Intervention (n=118)</th><th>Placebo (n=138)</th></tr>
<tr><td>Male - n (%)</td><td>54 (46%)</td><td>68 (49%)</td></tr>
<tr><td>Age - (mean, SD)</td><td>M: 61.2 (10.1)
F: 64.4 (9.5)</td><td>M: 60.5 (9.7)
F: 62.2 (12.4)</td></tr>
</table>

Groups were well matched for clinical characteristics at baseline (no significant differences in SBP, DBP, heart rate, severity of dyspnoea, arterial hypoxaemia, or previous or concomitant disease).

Echocardiography performed: n=106 (89.8%) intervention group and n=129 (93.5%) control group
Incidence of RVD: n=37 (31.4%) intervention group and n=43 (31.2%) control group
</td></tr>
<tr><td>Number of Patients</td><td>n=256 randomised</td></tr>
<tr><td>Intervention</td><td>n=118</td></tr>
</table>

Bibliographic reference	Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.
	Heparin and alteplase (Actilyse) IV bolus of 5000U of UFH given before randomisation. 100mg alteplase administered as 10mg bolus, followed by 90mg IV infusion over 2 hours. All received infusion of UFH starting at a rate of 1000U per hour, subsequently adjusted to maintain aPTT 2.0-2.5 times the upper limit of normal. Overlapping anticoagulant therapy on day 3 after randomisation, adjusted to maintain INR of 2.5 to 3.5
Comparison	n=138 Heparin and placebo IV bolus of 5000U of UFH given before randomisation. Placebo administered (matched to intervention drug). All received infusion of UFH starting at a rate of 1000U per hour, subsequently adjusted to maintain aPTT 2.0-2.5 times the upper limit of normal. Overlapping anticoagulant therapy on day 3 after randomisation, adjusted to maintain INR of 2.5 to 3.5
Length of follow up	End of hospital stay or day 30 after randomisation (whichever was first)
Location	Germany (49 centres)
Outcomes measures and effect size	Primary endpoint: - Composite of: In-hospital death or clinical deterioration requiring escalation of treatment after alteplase or placebo infusion was terminated. Treatment escalation defined as: infusion of catecholamine for persistent

Bibliographic reference	**Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.**

arterial hypotension or shock / secondary or rescue thrombolysis / endotracheal intubation / CPR / emergency surgical embolectomy / thrombus fragmentation by catheter.

Secondary endpoints:

- Recurrent pulmonary embolism (confirmed by V/Q scan, spiral computed tomography or pulmonary angiography)
- Major bleeding (inc. fatal bleeding; haemorrhagic stroke; drop in Hb by ≥4g/dL with or without need for red-cell transfusion)
- Ischaemic stroke (confirmed by CT or MRI scan)

Results

Primary outcome	**Intervention (n=118)**	**Placebo (n=138)**	**P value**
Composite: death from all causes or clinical deterioration requiring treatment escalation	13 (11.0%)	34 (24.6%)	0.006
Death from all causes[1]	4 (3.4%)	3 (2.2%)	0.71
Escalation of treatment :	12 (10.2%)	34 (24.6%)	0.004
- Catecholamine infusion for persistent hypotension or shock	3 (2.5%)	8 (5.8%)	0.33
- Secondary thrombolysis[2]	9 (7.6%)	32 (23.2%)	0.001
- ET intubation	3 (2.5%)	3 (2.2%)	0.85
- CPR	0	1 (0.7%)	1.0
- Embolectomy or thrombus fragmentation	0	1 (0.7%)	1.0

Notes:

[1] Cause of deaths: Intervention: 2 from PE, 2 from underlying disease; Placebo: 2 from PE, 1 from bleeding complication

[2] Unblinding of the study for patients who deteriorated was an explicit part of the protocol. This occurred in 41 (16%) of all cases. Previous administration of thrombolysis is likely to have been an important factor influencing decisions about who should get 'secondary thrombolysis' and accounts for the significant difference between groups on this outcome (7.6% vs 23.2%).

Bibliographic reference	**Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.**

Secondary outcomes	Intervention (n=118)	Placebo (n=138)	P value
Confirmed recurrent PE	4 (3.4%)	4 (2.9%)	0.89
Major bleeding - Fatal bleeding - Haemorrhagic stroke - Other major bleed	1 (0.8%) 0 0 1	5 (3.6%) 1 (0.7%) 0 4 (2.9%)	0.29
Ischaemic stroke	0	1 (0.7%)	1.0

Note: Probability of 30 day event-free survival was significantly higher in intervention than control groups, p=0.005

Determinants of relative risk of in-hospital death or escalation of treatment (proportional-hazards model)	RR (95%CI)	p value
Heparin and placebo vs heparin and alteplase	2.63 (1.32 to 5.26)	0.006
Age >70yrs vs ≤70yrs	2.29 (1.14 to 4.60)	0.02
Female vs male	2.68 (1.34 to 5.36)	0.005
Previous or concomitant disease (vs absence): - Cardiac disease - Pulmonary disease - Diabetes	 1.72 (0.82 to 3.61) 1.26 (0.65 to 2.43) 0.70 (0.36 to 1.37)	 0.15 0.48 0.30
SBP ≤100mmHg vs >100mmHg	1.50 (0.32 to 7.00)	0.60
Heart rate >100beats/min vs ≤100beats/min	1.42 (0.75 to 2.68)	0.28
Respiratory rate >24breaths/min vs ≤24breaths/min	1.50 (0.78 to 2.85)	0.22
Arterial hypoxaemia vs absence[3]	3.57 (1.55 to 8.20)	0.003

Notes:

[3] Arterial hypoxemia defined as partial pressure of arterial oxygen <70 mm Hg or severe dyspnoea requiring oxygen at a rate > 2L/min

Bibliographic reference	**Konstantinides S., et al. (2002) Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New Eng J Med 347: 1143 – 1150.**
Source of funding	Supported by Boehringer Ingelheim Pharma (manufacture Actilyse)
Comments	- Based on data from the Management Strategies and Prognosis of Pulmonary Embolism Registry calculated that 217 were needed in each group, power 80%, alpha 5%, detection of a 33% relative reduction (13% absolute reduction) in the primary end point - Study terminated early: interim analysis after enrolment of first 250 patients demonstrated statistically significant difference between groups on primary endpoint - Trial protocol permitted breaking randomisation code if additional emergency therapy was required for a patient whose condition was deteriorating - Blinding was broken and secondary thrombolysis administered as emergency treatment to 32/138 (23.2%) of placebo patients masking potentially important difference in outcomes (both in direction of harm and benefit) - Unclear whether all patients in the study met the review protocol criteria for 'objective evidence of RV dysfunction'. Study included patients with pulmonary hypertension, RVD or both. Only approximately 31% had echocardiographic confirmation of RVD. Between 10-55% in each group had various signs of RV strain on ECG but this is not identified in RP as objective evidence of RVD.

Bibliographic reference	**Becattini C., et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125:e82-e86**
Study type	RCT (phase II, multicentre, double-blind, placebo-controlled) Randomisation on 1:1 ratio, randomisation list generated in blocks of 4, allocation to treatment locally performed based on progressive treatment number
Aim	To assess the effect of tenecteplase on right ventricular dysfunction (RVD) in haemodynamically stable patients with pulmonary embolism (PE)
Patient characteristics	<u>Inclusion criteria:</u> - 18 to 85 years - objective diagnosis of PE (confirmed via multi-detector CT-scan, pulmonary angiography, high probability lung scan or intermediate probability lung scan + objectively confirmed DVT)

<table>
<tr><th>Bibliographic reference</th><th>Becattini C., et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125:e82-e86</th></tr>
<tr><td></td><td>
- onset of symptoms ≤10days
- normal BP (≥100 mm Hg)
- RVD at echocardiography performed within 24hours of PE diagnosis

<u>Exclusion criteria:</u>
- Chronic pulmonary hypertension, severe COPD, or hypotension
- Clinically relevant bleeding within last 6months, haemorrhagic diathesis, active peptic ulcer, arterial aneurysm or arterial/venous malformation, cancer at increased risk of bleeding, history of stroke, intracranial or spinal surgery
- Therapeutic doses of heparin for >72hours prior to randomisation or thrombolytic treatment within the previous 4days or glycoprotein IIb/IIIa antagonists within last 7days
- Oral anticoagulation or prolonged CPR (>10minutes) in last 2weeks
- Severe hepatic or renal failure, sub-acute bacterial endocarditis
- Pregnancy, lactation or delivery in 30days before randomisation

Significant difference between study groups in age and heart rate at baseline (see table below); no differences in gender, weight, BMI, diastolic BP, systolic BP, respiratory rate. Clinical presentation was similar between the two groups

<table>
<tr><th>Baseline characteristics:</th><th>Intervention (n=28)</th><th>Placebo (n=30)</th><th>p-value</th></tr>
<tr><td>Male - n (%)</td><td>13 (46.4%)</td><td>10 (33.3%)</td><td>ns</td></tr>
<tr><td>Age - mean ± SE</td><td>72.1 ± 1.2</td><td>64.5 ± 2.5</td><td>0.01</td></tr>
<tr><td>Heart rate (bpm) - mean ± SE</td><td>90.3 ± 2.9</td><td>102.0 ± 4.7</td><td>0.04</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>n = 58 (Intervention n=28; Placebo n=30)</td></tr>
<tr><td>Intervention</td><td>Tenecteplase + unfractionated heparin (UFH)

Tenecteplase (within 6 hours from baseline echocardiography);</td></tr>
</table>

Bibliographic reference	Becattini C., et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125:e82-e86
	- IV weight-adjusted bolus (over 5 seconds) - Dose ranging from 30 to 50mg with a 5mg step every 10kg (from <60 to ≥90kg) All participants received unfractionated heparin (80IU/kg IV bolus, followed by infusion of 18IU/kg/h). Bolus administration omitted for those already on heparin at time of inclusion in study. Heparin dose adjusted to achieve and maintain aPTT at 2.0-2.5 x control. Heparin continued until INR in the therapeutic range (2.0 to 3.0) in two consecutive days. Note: UFH was given concurrently with tenecteplase. Vitamin K antagonists were started on same day of study treatment administration or as soon as possible.
Comparison	Placebo + unfractionated heparin (UFH) Placebo (within 6hours from baseline echocardiography); - IV bolus All participants received unfractionated heparin (80IU/kg IV bolus, followed by infusion of 18IU/kg/h). Bolus administration omitted for those already on heparin at time of inclusion in study. Heparin dose adjusted to achieve and maintain aPTT at 2.0-2.5 x control. Heparin continued until INR in the therapeutic range (2.0 to 3.0) in two consecutive days. Vitamin K antagonists were started on same day of study treatment administration or as soon as possible.
Length of follow up	30 days
Location	Italy (15 centres)

Bibliographic reference	**Becattini C., et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125:e82-e86**
Outcomes measures and effect size	Primary end point: - Reduction of RVD at echocardiography 24hrs after randomisation (outcome not in review protocol) Secondary end points: - Reduction of RVD at 7 days or at hospital discharge (whichever was first) (outcome not in review protocol) - Clinical deterioration (the need for one or more of catecholamine infusion for sustained hypotension or shock, ET intubation, thrombolytic treatment, CPR, emergency surgical embolectomy or catheter fragmentation) requiring escalation of treatment within 7 days or before discharge - Recurrence of PE (objectively confirmed) at 30 days from randomisation - Death at 30 days from randomisation Safety study endpoints: - Major bleeding (fatal / intracranial / requiring transfusion or intervention for haemodynamic deterioration) within 7days from randomisation or before discharge - Serious adverse events (outcome not in review protocol) All had baseline and 24 hour echocardiography **Clinical outcomes:** <table><tr><th>Clinical event</th><th>Intervention (n=28)</th><th>Placebo (n=30)</th></tr><tr><td>All-cause mortality (within 30 days)</td><td>0</td><td>1 (day 5)</td></tr><tr><td>Major bleeding</td><td>2 (1 intracranial; 1 gastrointestinal)</td><td>1 (abdominal haematoma)</td></tr><tr><td>Clinical deterioration requiring CPR</td><td>0</td><td>1 (day 3)</td></tr><tr><td>Death due to PE</td><td>0</td><td>0</td></tr><tr><td>Recurrence of PE</td><td>1 (day 3)</td><td>1 (day 9)</td></tr><tr><td>Minor bleeding</td><td>13</td><td>1</td></tr></table> Notes: • None of the following events occurred in a patient > 75yrs: death, major bleeding or clinical deterioration • Major bleeding events were non-fatal

Bibliographic reference	**Becattini C., et al. (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thrombosis Research 125:e82-e86**
	• 1 patient in intervention group and 1 patient in placebo group received over-anticoagulation in the 2-3 days prior to a major bleeding event • Echocardiographic indices of RVD reduction within first 24hrs were statistically significant, favouring tenecteplase over placebo; difference in RVD reduction was not significant after 7 days (outcome not in RP)
Source of funding	Grant from Boehringer Ingelheim, Italy to the Clinical Research Unit of the University of Perugia
Comments	- No loss to follow-up at 30 days - Study was initially designed to include 180 participants - Study terminated early because of feasibility issues re: access to dedicated round-the-clock echocardiography, and because PEITHO study was due to start (wanted to have outcome information available and convey eligible patients to PEITHO, which had improved study design) - Intervention group were significantly older and had lower heart rate profile than placebo group

Bibliographic reference	**Fasullo S., et al. (2011) Six-month echocardiographic study in patients with submassive pulomonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341:33-39**
Study type	RCT (double-blinded, placebo-controlled) Randomisation using preliminary computer algorithm; assessment of all patients at admission, before echocardiogram and before lung spiral CT by an external team of physicians (at least 2) who were blinded to the study protocol
Aim	To assess the effect of thrombolysis on RVD in haemodynamically stable patients with submassive PE and if thrombolysis could be more effective than anticoagulation with heparin inpatients with first episode of submassive PE
Patient characteristics	Recruitment: January 2005 to June 2009, consecutive patients with a first episode of submassive PE

Bibliographic reference	**Fasullo S., et al. (2011) Six-month echocardiographic study in patients with submassive pulomonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341:33-39**

Inclusion criteria:

- 18 to 75years
- First episode submassive PE
- Symptom onset ≤6hours
- normal BP (>100 mg hg)
- RVD at echocardiogram, positive lung spiral computed tomography
- Dyspnoea, chest pain, tachypnoea, hypoxaemia, oxygen saturation <90% in room air, D-dimer elevation, ECG with S1-Q3-T3 pattern, inversion of T waves in V1 to V4, a right bundle branch (RBB) or right axis deviation

Exclusion criteria:

- Active internal bleeding, recent intracranial bleeding, intracranial tumour or seizure history
- Ischaemic stroke <2months, neurosurgery in the last month, surgery within last 10 days, trauma within last 15 days, uncontrolled hypertension, haemorrhagic disorder of thrombocytopenia
- Severe impaired hepatic or renal function, GI bleeding within 10 days
- Pregnancy
- Arterial aneurysm or arterial/venous malformation, cancer at increased risk of bleeding
- Chronic pulmonary hypertension (CTEPH) or severe COPD who had received therapeutic doses of heparin for >72hours before randomisation
- Thrombolytic treatment within last 4 days, glycoprotein IIb/IIIa antagonists within last 7 days
- Taking oral anticoagulation

At baseline groups were well matched on: age, sex, respiratory rate, systolic BP, PO_2, PCO_2, pH, HCO_3, SaO_2 (room air), heart rate, thoracic pain, syncope, cyanosis, sweats, jugular congest, helical computed tomography, S 1-Q3, cRBBB, IRBBB, inverted T wave, echocardiograph RVD.

Baseline demographic characteristics:	**Intervention (n=37)**	**Placebo (n=35)**
Male - n (%)	21 (56.8%)	20 (57.1%)
Age (mean, SD)	55 (16.7)	57 (15.5)

Bibliographic reference	**Fasullo S., et al. (2011) Six-month echocardiographic study in patients with submassive pulomonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341:33-39**
	Previous or concomitant diseases at admission were similar in both groups.
Number of Patients	n=72 (n=37 intervention, n=35 placebo)
Intervention	Alteplase + UFH 100mg of alteplase (Actilyse); 10mg bolus followed by 90mg IV infusion over 2 hours Before randomisation all received a bolus of 5000 IU heparin, were randomised and continued heparin infusion. After administration of intervention/placebo, both groups continued UFH 1000 IU/hr and/or based on aPTT, in combination with warfarin (started 1 day after randomisation) until INR was within the therapeutic range for 2 consecutive days. Heparin was then stopped, warfarin continued after discharge and during follow-up.
Comparison	Matched placebo + UFH Before randomisation all received a bolus of 5000 IU heparin, were randomised and continued heparin infusion. After administration of intervention/placebo, both groups continued UFH 1000 IU/hr and/or based on aPTT, in combination with warfarin (started 1 day after randomisation) until INR was within the therapeutic range for 2 consecutive days. Heparin was then stopped, warfarin continued after discharge and during follow-up.
Length of follow up	6 months
Location	Italy – 3 centres
Outcomes measures and effect size	Primary endpoint: - Reduction of RVD (outcome not in review protocol) Secondary endpoints: - Recurrence of PE or death - Clinical events during hospitalisation and at 180 days from randomisation

Bibliographic reference	**Fasullo S., et al. (2011) Six-month echocardiographic study in patients with submassive pulomonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341:33-39**

Study safety endpoints:

- Major bleedings before discharge
- Serious adverse events (outcome not in review protocol)

Clinical outcomes:

In-hospital clinical events (first 10 days)	**Intervention (n=37)**	**Placebo (n=35)**	**p-value**
Death from all causes (n, %) - Recurrent PE - Irreversible RVD	0 0 0	5 (14.2%) 3 (8.5%) 2 (5.7%)	0.055 NS NS
Major bleeding	2 (5.4%) (1 heamaturia; 1 gastrointestinal)	1 (2.9%) (abdominal)	NS
Minor bleeding	11 (29.7%)	4 (11.4%)	0.20

Post-discharge and during follow-up clinical events (180 days)	**Intervention (n=37)**	**Placebo (n=35)**	**p-value**
Death from all causes (n, %) - Recurrent PE (fatal)	0 0	1 (2.9%) 1 (2.9%)	NS NS
Recurrent PE (non-fatal)	0	1 (2.9%)	NS
RVD deterioration (requiring hospitalisation)	0	3 (8.5%)	NS
Minor bleeding	5 (13.5%)	4 (11.4%)	NS
DVT persistence	0	5 (14.2%)	0.055

Total cumulative clinical events (during hospitalisation and follow-up)	**Intervention (n=37)**	**Placebo (n=35)**	**p-value**

Bibliographic reference	**Fasullo S., et al. (2011) Six-month echocardiographic study in patients with submassive pulomonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. The American Journal of the Medical Sciences 341:33-39**

Death from all causes (n, %) - Recurrent PE - Irreversible RVD	0 0 0	6 (17.1%) 4 (11.4%) 2 (5.7%)	0.027
Major bleeding	2 (5.4%)	1 (2.9%)	NS
Minor bleeding	16 (43.2%)	8 (22.0%)	0.005
Recurrent PE (non-fatal)	0	1 (2.9%)	NS
RVD deterioration (requiring hospitalisation)	0	3 (8.6%)	NS
DVT persistence	0	5 (14.2%)	0.055
Total events (exc. minor bleeding)	2 (5.4%)	16 (45.7%)	0.005

Note: All 3 patients who had major bleeding had supratherapeutic prolongation of the aPTT (>100 seconds), probably related to heparin overdosing

Source of funding	Not reported
Comments	- Sample size calculation: 32 was assumed as the minimum per group for this study

Bibliographic reference	**Sharifi M., et al. (2013). Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiology 111:273-277.**
Study type	RCT Open-label study; centralised randomisation (no details of method of sequence generation); allocation concealment maintained (sealed envelopes).
Aim	To assess the effects of low-dose tissue plasminogen activator (tPA) on pulmonary artery systolic pressure in patients with 'moderate' PE at 28 months.

<table>
<tr><td>Bibliographic reference</td><td>Sharifi M., et al. (2013). Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiology 111:273-277.</td></tr>
<tr><td>Patient characteristics</td><td>Recruitment: May 2008 to March 2010

<u>Inclusion criteria:</u>
- Adult patients
- Signs & symptoms of PE, plus either CT angiographic involvement of >70% of thrombus in ≥2 lobar or main pulmonary arteries, or ventilation/perfusion scan showing mismatch in ≥2 lobes
- Onset of symptoms ≤10days

<u>Exclusion criteria:</u>
- >8 hours since start of parenteral anticoagulation
- Systolic BP <95 or ≥200/100 mm Hg
- Eligible for full-dose thrombolysis
- Contraindicated for UFH or LMWH or inability to perform echocardiography due to chest deformity/bandages/catheters
- Severe thrombocytopenia or major bleeding within <2 months requiring tansfusion
- Surgery or major trauma within <2 weeks
- Brain/neurological surgery, ICH or subdural haematoma within <1 year
- End-stage conditions

<table><tr><th>Baseline demographic characteristics:</th><th>Intervention (n=61)</th><th>Control (n=60)</th></tr><tr><td>Male - n (%)</td><td>28 (46%)</td><td>27 (45%)</td></tr><tr><td>Age (mean, SD)</td><td>58 (9)</td><td>59 (10)</td></tr></table>
No significant differences between groups on any demographic or baseline clinical characteristics, including measures of RV dysfunction/strain.</td></tr>
<tr><td>Number of Patients</td><td>Randomised n=121 (Intervention: n=61; Control n=60)

<u>Attrition:</u>
Intervention: 2/60 (3%) surviving patients lost to 28 month follow-up</td></tr>
</table>

Bibliographic reference	**Sharifi M., et al. (2013). Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiology 111:273-277.**
	Control: 1/57 (2%) surviving patients lost to 28 month follow-up
Intervention	Tissue plasminogen activator (tPA) + anticoagulation (LMWH / UFH) Thrombolysis: 'Low dose' tPA (Alteplase) – defined as ≤50% of standard dose (100mg) commonly used for treating PE. For patients weighing ≥50kg: total dose = 50mg given as 10mg IV bolus followed by 40mg infusion over 2 hours. Anticoagulation: - 48/61 (79%) received LMWH (enoxaparin 1mg/kg) given subcutaneously twice daily with initial dose not to exceed 80mg - 13/61 (21%) received UFH at 70 U/kg as a bolus (not to exceed 6,000 U), with subsequent dose adjustment to keep aPTT at 1.5-2 times baseline value. Maintenance dose of UFH kept at 10U/kg/hour (not to exceed 1,000 U/hour) until 3 hours after termination of tPA infusion, when it was increased to 18 U/kg/hour. UFH administration was determined by presence of renal insufficiency or patient preference. Warfarin was started in all patients at admission.
Comparison	Anticoagulation only - 49/60 patients (82%) received LMWH (enoxaparin 1mg/kg) given subcutaneously twice daily - 11/60 (18%) received UFH at 80 U/kg as a bolus followed by 18 U/kg/hour with target aPTT at 1.5-2 times baseline value. UFH administration determined by presence of renal insufficiency or patient preference. Warfarin was started in all patients at admission.
Length of follow up	In hospital for secondary outcomes; 840 days (28 months) for primary outcomes

Bibliographic reference	**Sharifi M., et al. (2013). Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiology 111:273-277.**
Location	USA (one centre)
Outcomes measures and effect size	Primary endpoints (at 28 months): - Pulmonary hypertension (pulmonary artery systolic pressure ≥40 mm Hg assessed by echocardiography, performed before then 24-48 hours after tPA administration and then at 6-monthly intervals) - Composite of pulmonary hypertension and recurrent PE (outcome not in review protocol) Secondary endpoints (in hospital): - Recurrent PE - Total mortality - Composite total mortality plus recurrent PE - Length of hospital stay - Bleeding (not defined)

Primary endpoints at 28 months	**Intervention (n=58)**	**Control (n=56)**	**p-value**
Pulmonary hypertension	9 (16%)	32 (57%)	<0.001
Composite: Pulmonary hypertension plus recurrent PE	9 (16%)	35 (63%)	<0.001
Secondary endpoints – in hospital	**Intervention (n=61)**	**Control (n=60)**	**p-value**
Recurrent PE	0	3 (5%)	0.08
Total mortality[1]	1 (1.6%)	3 (5%)	0.30
Composite: Total mortality plus recurrent PE	1 (1.65)	6 (10%)	0.049
Hospital stay (days) – mean (SD)	2.2 (0.5)	4.9 (0.8)	<0.001
Bleeding	0	0	-

[1] No details given of cause of deaths

Bibliographic reference	**Sharifi M., et al. (2013). Moderate pulmonary embolism treated with thrombolysis (from the MOPETT trial). Am J Cardiology 111:273-277.**
Source of funding	Not reported
Comments	- Not all patients may match the review protocol because objective evidence of RVD was not a requirement for enrolment: 21% had echocardiographic evidence of RV enlargement; 6% had RV hypokinesia; 68% had elevated BNP / troponin I but unclear if these are mutually exclusive - Open label study - only a cardiologist assessing echocardiographic images for evidence of pulmonary hypertension was blinded to treatment allocation - Power calculation estimated 60 patient were required per group

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**
Study type	RCT (double-blinded, placebo-controlled) Blocked 1:1 randomised sequence prepared by statistician Treatment allocation by sealed envelope containing unique ID number used by study pharmacist to prepare treatment/placebo drug according to a file kept locked in pharmacy
Aim	To test if tenetceplase increases the probability of a favourable composite patient-oriented outcome after submassive PE
Patient characteristics	Recruitment: August 2008 to October 2012 <u>Inclusion criteria:</u>

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**

- Age >17yrs
- PE diagnosed via CT pulmonary angiography within 24hrs
- Normal arterial systolic BP ≥90mm Hg
- Evidence of RVD: (i) hypokinesis on echocardiography or (ii) elevated Troponin I or T or (iii) brain natriuretic peptide (BNP) measurement > 90 pg ml / NT proBNP >900pg/ml

Exclusion criteria:

- Systolic hypotension (<90 mmHg)
- Systemic fibrinolysis within past 7 days
- Inability to walk several blocks
- Documented GI bleed within past 30 days or active bleeding at enrolment (intraperitoneal / retroperitoneal / pulmonary / uterine / bladder / nose or head trauma); known inherited bleeding disorder
- History of stroke within the past 12 months
- Chest, abdominal, intracranial or spinal surgery within past 14 days
- Contraindications to fibrinolysis
- End-stage conditions
- Pregnancy

No significant differences between study groups on demographic or clinical characteristics, including frequency or location of DVT, although data suggested a trend (p<0.10) in relation to gender and malignancy (see table below)

Baseline characteristics:	**Intervention (n=40)**	**Placebo (n=43)**	**p-value**
Male - n (%)	20 (50%)	29 (67%)	0.09
Age (mean, SD)	57 (14)	54 (14)	0.38
aged >75yrs – n (%)	4 (10%)	4 (9%)	0.99
Active malignancy (on-going oncology care) – n (%)	9 (23%)	4 (9%)	0.08

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**
	- Malignancy under chemotherapy – n (%): 5 (12.5%) / 0 / 0.01 No difference between groups in terms of quality of anticoagulation in 3 months after discharge assessed by the time in therapeutic range (TTR), defined as % of INR measurements found to be between 2 and 3 within 1 week after discharge and 90-day follow-up: - treatment group mean TTR 48% (SD 24%), median TTR 50% (1st – 3rd quartile range 33-67%) - placebo group mean TTR 49% (SD 20%), median TTR 50% (1st – 3rd quartile range 33-60%)
Number of Patients	n=83 (Intervention n=40; Placebo n=43) Loss to 90-day follow-up: Intervention : 2/39 (5%) surviving patients, Placebo: 3/42 (7%) surviving patients
Intervention	Single IV bolus of tenecteplase + low-molecular-weight heparin (LMWH) Full dose low-molecular-weight-heparin (1 mg/kg enoxaparin or 200 units/kg dalteparin) administered subcutaneously prior to injection of study drug. LMWH was continued for duration of hospital stay. Patients already on unfractionated heparin were switched to LMWH. Tiered (weight-based) dose of TKNase (tenecteplase) administered as soon as practicable, as follows:

Patient weight (kg)	Volume (mL)	Tenecteplase (mg)	NaCl (mg)
<60	6	30	540
≥60 to <70	7	35	630
≥70 to <80	8	40	720
≥80 to <90	9	45	810
≥90	10	50	900

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**
	After discharge, patients without active cancer were treated with warfarin sodium with target INR for prothrombin time between 2 and 3. Patients with active cancer were treated with LMWH injections.
Comparison	IV bolus placebo+ low-molecular-weight heparin (LMWH) Full dose low molecular-weight-heparin (enoxaparin or weight-based dalteparin) administered subcutaneously prior to injection of placebo. LMWH was continued for duration of hospital stay. Patients already on unfractionated heparin were switched to LMWH. Placebo administered in identical opaque syringe to study drug as soon as practicable. After discharge, patients without active cancer were treated with warfarin sodium with target INR for prothrombin time between 2 and 3. Patients with active cancer were treated with LMWH injections.
Length of follow up	90 days
Location	USA – 8 academic medical centres
Outcomes measures and effect size	Primary outcome: Composite adverse outcome, as follows: Within 5 days - PE-related: death; circulatory shock (hypotension requiring vasopressor infusion); intubation - Treatment-related: death from haemorrhage; major bleeding (intracranial / intraspinal, or active bleeding requiring transfusion, surgery, endoscopic or intravascular treatment) At 90 days: - VTE recurrence - PE and DVT (confirmed via imaging) - Poor functional capacity: RVD confirmed via echocardiograph, plus either exercise intolerance (inability to walk 330m using 6 minute walk test) or dyspnoea at rest (New York Heart Association functional score ≥3)

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**

- QoL: 'Low perception of wellness' (defined as SF-36 Physical component summary score < 30)

Clinical outcomes:

Clinical event	**Intervention (n=40)**	**Placebo (n=43)**
Within 5 days All-cause mortality: - PE-related - Treatment related	 0 1 (intracranial bleed)	 1 0
Major bleeding	1 (ICH resulting in death)	0
Clinical deterioration (shock / intubation)	0	2
	Intervention (n=37)	**Placebo (n=39)**
At 90 days: Recurrent VTE: - PE only - DVT only - Both PE and DVT	 0 0 1	 2 1 1
Quality of Life (SF-36 Physical Component Summary score <30)	1	10
Poor functional capacity (confirmed RVD, plus either exercise intolerance or dyspnoea at rest)	4	8

Source of funding	Funded by investigator-initiated grant from Genentech, Inc. who manufacture TKNase (tecencteplase) and supplied the study drug but were not involved in study design or data analysis.

Bibliographic reference	**Kline J., et al. (2014) Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicentre double-blind, placebo-controlled randomized trial. J Thrombosis and Haemostasis 12: 459-468** **(additional detail from Kline et al. (2013) Rationale and methodology for a multicentre randomised trial of fibrinolysis for pulmonary embolism that includes quality of life outcomes. Emergency Medicine Australasia 25: 515-526.)**
Comments	- No lockout on symptom duration, but enrolment was within 24hrs of PE diagnosis by CT pulmonary angiography - No details of randomisation block size - Blinding was broken when clinical staff opened envelope to reveal group allocation in 2 (5%) patients treated with tenecteplase (both had serious adverse outcome that prompted unblinding) and 3 (7%) treated with placebo (2 had a serious adverse outcome). No details of additional therapy given to these patients. - 6% loss to 3month follow-up among survivors - Study underpowered (intended to recruit 82 per group) - trial terminated early due to primary investigator relocating leading to “insurmountable legal and administrative barriers”

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**
Study type	RCT (double-blind, placebo-controlled) Central computerised randomisation, stratified by centre, within centres in blocks of 4 for equal distribution of the treatment groups. Allocation concealment maintained.
Aim	To assess the clinical efficacy and safety of a single-bolus injection of tenecteplase in addition to standard anticoagulation therapy compared with placebo in normotensive patients with acute pulmonary embolism and evidence of RV dysfunction.
Patient characteristics	Recruitment: November 2007 to July 2012

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**

Inclusion criteria:

- ≥18years
- Objectively confirmed acute PE
- Onset of symptoms ≤15 days before randomisation
- Evidence of RVD confirmed by echocardiography or spiral computed CT of the chest
- Evidence of myocardial injury confirmed by positive test for troponin I or troponin T

Exclusion criteria:

- Haemodynamic collapse at presentation
- Known significant bleeding risk
- Administration of thrombolytic agent or vena cava filter insertion or pulmonary thrombectomy in the previous 4days
- Uncontrolled hypertension (systolic BP >180 mm Hg and/or diastolic >110 mm Hg)
- Hypersensitivity to tenecteplase, alteplase, UFH or any excipients
- Pregnancy, lactation, parturition in the last 30 days
- Known coagulation disorder

Baseline demographic characteristics:	**Intervention (n=506)**	**Placebo (n=499)**
Male - n (%)	242 (47.8%)	231 (46.3%)
Age (mean, SD)	66.5 (14.7)	65.8 (15.9)
Heart rate (bpm, SD)	94.5 (17.1)	92.3 (16.7)
LMWH / fondaparinux given before randomisation (n, %)	170 (33.6%)	133 (26.6%)

<table>
<tr><td>Bibliographic reference</td><td>Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11
(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)</td></tr>
<tr><td></td><td>Demographic data, clinical status at baseline and medical history were well matched between the two treatment groups (between-group differences were non-significant except for heart rate (p=0.05) and LMWH / fondaparinux given before randomisation (p=0.02)).</td></tr>
<tr><td>Number of Patients</td><td>n=1006 randomised (n=1 consent form unable to be found, ITT population n=1005);
Intervention n = 506; Placebo n = 499</td></tr>
<tr><td>Intervention</td><td>Single, weight-based, IV bolus (over 5 to 10 seconds) of tenecteplase + UFH

Weight-based IV bolus of tenecteplase as follows:

<table>
<tr><th>Patient weight (kg)</th><th>Volume (mL)</th><th>Dose (mg)</th><th>Dose (Units)</th></tr>
<tr><td><60</td><td>6</td><td>30</td><td>6000</td></tr>
<tr><td>≥60 to <70</td><td>7</td><td>35</td><td>7000</td></tr>
<tr><td>≥70 to <80</td><td>8</td><td>40</td><td>8000</td></tr>
<tr><td>≥80 to <90</td><td>9</td><td>45</td><td>9000</td></tr>
<tr><td>≥90</td><td>10</td><td>50</td><td>10,000</td></tr>
</table>

IV bolus of unfractionated heparin (UFH) administered immediately after randomisation (both groups) at a dosage of 80 IU/kg body weight. (Note: IV bolus not given to those who had already had a UFH bolus or infusion; in those who were receiving a therapeutic dose of LMWH or fondaparinux, IV bolus of UFH not given and infusion was delayed until 12hrs after last injection of LMWH or 24hrs after last injection of fondaparinux).
Heparin continued as infusion, rate adjusted to achieve an aPTT that was 2.0 to 2.5 time the upper limit of the normal range.

Other anticoagulant agents not allowed until 48 hours after randomisation</td></tr>
</table>

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**
Comparison	Placebo single bolus of the same volume and appearance as the bolus of tenecteplase + UFH IV bolus of unfractionated heparin (UFH) administered immediately after randomisation (both groups) at a dosage of 80 IU/kg body weight. (Note: IV bolus not given to those who had already had a UFH bolus or infusion; in those who were receiving a therapeutic dose of LMWH or fondaparinux, IV bolus of UFH not given and infusion was deleayed until 12hrs after last injection of LMWH or 24hrs after last injection of fondaparinux). Heparin continued as infusion, rate adjusted to achieve an aPTT that was 2.0 to 2.5 time the upper limit of the normal range. Other anticoagulant agents not allowed until 48 hours after randomisation
Length of follow up	30 days
Location	13 countries (76 sites) across Europe and North America
Outcomes measures and effect size	Primary outcome: - Clinical composite of death from any cause or haemodynamic decompensation (or collapse) within 7days after randomisation. Haemodynamic decompensation defined as: requiring CPR / drop in systolic BP <90 mm Hg for at least 15mins / drop in systolic BP of at least 40 mm Hg for at least 15 mins with signs of end-organ hypofusion / requiring catecholamines. Secondary outcomes: - Death within 7 days after randomisation - Haemodynamic compensation within 7 days after randomisation (defined as above) - Image-confirmed symptomatic recurrence of PE within 7 days - Death within 30 days

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**

Safety outcomes:

- Ischaemic or haemorrhagic stroke within 7 days after randomisation
- Other (extracranial) moderate or severe bleeding within 7 days – requiring transfusion or leading to haemodynamic compromise or death
- Serious adverse events (SAEs) within 30 days (outcome not in review protocol)

Clinical efficacy outcomes:	**Intervention, n=506**	**Placebo, n=499**	**OR (95%CI), p value**
Primary outcome (composite) within 7 days	13 (2.6%)	28 (5.6%)	0.44 (0.23 to 0.87), 0.02
- Haemodynamic decompensation	8 (1.6%)	25 (5.0%)	0.30 (0.14 to 0.68), 0.002
- Death from any cause	6 (1.2%)	9 (1.8%)	0.65 (0.23 to 1.85), 0.42
○ From haemodynamic collapse	1	3	
○ From recurrent PE	0	3	
○ From stroke	4	0	
○ From bleeding	1	0	
○ Other cause of death	0	3	
Recurrent PE (from randomisation to day 7)	1 (0.2%)	5 (1.0%)	0.20 (0.02 to 1.68), 0.12
- Fatal	0	3 (0.6%)	
- Non-fatal	1 (0.2%)	2 (0.4%)	
Other in-hospital complications/procedures			
- Mechanical ventilation	8 (1.6%)	15 (3.0%)	
- Surgical embolectomy	1 (0.2%)	2 (0.4%)	
- Catheter venous fragmentation	1 (0.2%)	0	
- Vena cava interruption	5 (1.0%)	1 (0.2%)	
- Other thrombolytic treatment	4 (0.8%)	23 (4.6%)	
Death, any cause (randomisation to day 30):	12 (2.4%)	16 (3.2%)	0.73 (0.34 to 1.57), 0.42

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**

○ From haemodynamic collapse ○ From recurrent PE ○ From respiratory failure ○ From stroke ○ From bleeding ○ Other cause of death	1 1 0 5 2 3	3 3 3 1 0 6	
Still hospitalised at day 30	59 (11.7%)	50 (10.0%)	
Rehospitalisation (randomisation to day 30)	22 (4.4%)	15 (3.0%)	

Safety outcomes:	**Intervention, n=506**	**Placebo, n=499**	**OR (95%CI), p value**
Bleeding (from randomisation to day 7) - Major extracranial bleeding - Minor bleeding	 32 (6.3%) 165 (32.6%)	 6 (1.2%) 43 (8.6%)	5.55 (2.3 to 13.39), <0.001
Stroke (from randomisation to day 7) - Ischaemic - Haemorrhagic (inc. haemorrhagic transformation of ischaemic stroke)	12 (2.4%) 2 (0.4%) 10 (2.0%)	1 (0.2%) 0 1 (0.2%)	12.10 (1.57 to 93.39), 0.003

Pre-specified subgroup analyses:

Outcome: death or haemodynamic decompensation	**Intervention (n=506)**	**Placebo (n=499)**	**OR (95%CI)**	**p-value for interaction**
Age				p=0.36
- ≤75years	6/344 (1.7%)	17/335 (5.1%)	0.33 (0.13 to 0.85)	

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**

- >75years	7/162 (4.3%)	11/164 (6.7%)	0.63 (0.24 to 1.66)	
Sex				p=0.90
- Male	7/242 (2.9%)	14/231 (6.1%)	0.46 (0.18 to 1.16)	
- Female	6/264 (2.3%)	14/268 (5.2%)	0.42 (0.16 to 1.12)	
Outcome: major extracranial bleeding	**Intervention (n=506)**	**Placebo (n=499)**	**OR (95%CI)**	
Age				p=0.09
- ≤75years	14/344 (4.1%)	5/335 (1.5%)	2.80 (1.00 to 7.86)	
- >75years	18/162 (11.1%)	1/164 (0.6%)	20.38 (2.69 to 154.53)	
Sex				p=0.13
- Male	11/242 (4.5%)	4/231 (1.7%)	2.70 (0.85 to 8.61)	
- Female	21/264 (8.0%)	2/268 (0.7%)	11.49 (2.67 to 49.53)	

Source of funding	Public funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique) & German Federal Ministry of Education and Research, plus additional grant support from Boehringer Ingelheim (market authorisation holder of tenecteplase) who supplied the tenecteplase and placebo used for the study. An early version of the manuscript was sent to a representative of Boehringer Ingelheim before submission.
Comments	- Efficacy and safety analysis ITT - Protocol permitted unblinding in event of emergency. Open-label secondary thrombolysis was given to 27 patients (2.6%) - significantly more of the control group compared with the intervention group (4.6% vs 0.8%) - Prespecified subgroup analysis; age, sex, country of recruitment - A blinded, centralised Critical Event Committee adjudicated on classification of all critical events (death, haemodynamic collapse, recurrent PE, major bleeding, and stroke).

Bibliographic reference	**Meyer G., et al. (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402-11** **(additional detail from The Steering Committee (2012) Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 163:33-38.e1)**
	- Based on a meta-analysis of previous thrombolysis trials and large PE trial, estimated that the primary end point in the control group would be 7%, 0.047 2-sided significance level, power 80% - total number needed in the study = 948 - A 6 month follow-up is planned (not yet reported) measuring: death (including cause of death); functional status and severity of dyspnoea using New York Heart Association scale; pulmonary artery pressure; persistent RVD

G.2 Review question 2: Compression stockings for PTS prevention

G.2.1 Clinical evidence tables

Bibliographic reference	**Brandjes et al (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. The Lancet 349:759-762**
Study type	RCT (randomisation via sealed envelope in blocks of 8; open-label, outcome assessor blinded)
Aim	Study aim; to document prospectively the cumulative rate of PTS after the first episode of proximal DVT and assess the preventive effect of direct application of a sized-to-fit graded compression stocking
Patient characteristics	Consecutive outpatients referred by family doctors to a medical centre Inclusion criteria; - a first episode of venogram-proven proximal DVT Exclusion criteria; - life expectancy <6months - paralysis of the leg, bilateral thrombosis, leg ulcers or extensive varicosity - current use of compression stockings

Bibliographic reference	Brandjes et al (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. The Lancet 349:759-762
	groups considered well matched at baseline for age, days since onset of symptoms, gender, underlying disorders, idiopathic thrombosis, location of thrombus
Number of Patients	N=194 randomised
Intervention	N=96 2 pairs of below-knee elastic compression stockings, 40mmHg at the ankle, 36mmHg lower calf, 21mmHg upper calf (replaced every 6months) – made-to-measure (Neo Durelna, Varitex, Haarlem, Netherlands) Applied 2 to 3weeks after first episode of proximal DVT – to wear daily All had initially had heparin treatment in hospital
Comparison	N=98 No compression stockings All had initially had heparin treatment in hospital
Length of follow up	All followed-up for ≥60months, median 76months (range 60 to 96) Every 3moths for first 2years, 6monthly after for ≤5years
Location	The Netherlands
Outcomes measures and effect size	Definition of PTS; used previously defined clinical characteristics and objective leg measurement; pain in the calf during rest or on standing or walking, increase in leg circumference, new varicosis or venous ulcers – scored and recorded on a specially designed form that combined components of earlier scoring systems. Scoring forms interpreted by independent adjudication, unaware of treatment allocation. Used to define as mild-to-moderate PTS and severe PTS Diagnosis made only after 6months to differentiate between PTS symptoms and those associated with initial thrombotic event Primary outcome; - cumulative incidence of mild-to-moderate PTS Lost to follow-up; N= 4 (intervention), N=2 (control) N=19 (intervention), N=16 (control) died Compliance; 4-point compliance scale used via nurse interviews; wearing always, usually (>80%), sporadically, never

Bibliographic reference	Brandjes et al (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. The Lancet 349:759-762
	Results **Cumulative incidence of mild-to-moderate PTS**; - N=19 (20%) intervention, N=46 (47%) control, p<0.001* Other outcomes reported; Severe PTS*; N=11 (11%) intervention, N=23 (23%) control, p<0.001 Venous ulceration; N=4/96 (N=3 intervention, N=1/96 control) Developed severe PTS after initial mild-to-moderate PTS; N=6 Recurrence of VTE; N=14/96 (14.6%) intervention, N=13/98 (13.3%) intervention, difference NS (*most developed PTS within first 24months) Compliance; - N=7/96 did not wear/only occasionally wore - N=16/96 usually wore - N=73/96 always wore
Source of funding	Not stated
Comments	Little information about PTS incidence, assumed cumulative 6year rate of mild-to-moderate of ≥40% without stockings, N=100 needed in each group for 80%power, 0.05 significance level to detect a 50% reduction with compression stockings

Bibliographic reference	Prandoni et al (2004) Below-knee compression stockings to prevent the post-thrombotic syndrome. Ann Intern Med 141:249-256
Study type	RCT (randomisation in blocks of 20 to either group, assignment based on a computer generated list accessible only to a trial nurse; open-label)
Aim	Study aim; to compare the 5year cumulative incidence of PTS in patients assigned elastic stockings compared to those who were not
Patient characteristics	Consecutive patients referred to internal medicine department, January 1997 to March 2000, at discharge Inclusion criteria;

Bibliographic reference	Prandoni et al (2004) Below-knee compression stockings to prevent the post-thrombotic syndrome. Ann Intern Med 141:249-256
	- Clinically symptomatic proximal DVT, confirmed by compression ultrasonography Exclusion criteria; - Recurrent ipsilateral DVT, pre-existing leg ulcers or signs of chronic venous insufficiency, bilateral thrombosis - Short life expectancy - Contraindication for using stockings
Number of Patients	N=180 randomised
Intervention	N=90 Elastic below-knee compression stockings at hospital discharge (average 1week after admission, range 5 to 10days) 30 to 40mmHg at the ankle, to wear during the day for ≥2years Available in 5 sizes, 2pairs, replaced every 6months (New Medical Services, Linea Flebologica Flebysan, Rovigo, Italy) All received initial treatment with heparin followed by vitamin K antagonists
Comparison	N=90 No stocking All received initial treatment with heparin followed by vitamin K antagonists
Length of follow up	Up to 5years Intervention; mean follow-up 50.5months, median 54months (range 7 to 60) Control; mean follow-up 47.5months, median 52months (range 6 to 60)
Location	Italy
Outcomes measures and effect size	Definition of PTS; scored using a standardised scale, scored 5 leg symptoms and 6 objective signs, assessors not aware of treatment allocation or previous measurements, scale had previously been demonstrated to have high interobserver agreement and high sensitivity and specificity for discriminating PTS and mild versus severe Primary outcome; - Cumulative incidence of PTS

Bibliographic reference	Prandoni et al (2004) Below-knee compression stockings to prevent the post-thrombotic syndrome. Ann Intern Med 141:249-256

Lost to follow-up; N= 1 (intervention), N=2 (control)
N=7 (intervention), N=12 (control) died

Adherence;
Patient reported notebooks
Considered satisfactory for ≥80% of daytime hours

Results
Cumulative incidence of PTS;
PTS; N=23/90 intervention (N=3 severe), N=44/90 control (N=10 severe)
Cumulative incidence;

	After 6months (95%CI)	After 1year (95%CI)	After 2years (95%CI)	After 3years (95%CI)	
Intervention	21.1% (12.7 to 29.5)	22.2% (13.8 to 30.7)	24.5% (15.6 to 33.4)	25.7% (16.6 to 34.7)	Stable after 3years
Control	40% (29.9 to 50.1)	46.7% (36.4 to 57.0)	49.1% (38.7 to 59.4)	-	Stable after 2years

Cumulative incidence of severe PTS at the end of follow-up;
- Intervention 3.5% (0 to 7.3)
- Control 11.7% (4.8 to 18.6)

HR (95%CI) intervention compared with control; 0.47 (0.28 to 0.79), p=0.004
Adjusted HR* (95%CI) ; 0.49 (0.29 to 0.84), p=0.011
NNT (95%CI); 4.3 (2.8 to 10.8)

PTS symptom severity;

	Intervention				Control		
	Mild	Moderate	Severe		Mild	Moderate	Severe
3mths (N=90)	59	31	0	3mths (N=90)	36	52	2
6mths (N=90)	54	36	0	6mths (N=90)	38	50	2

Bibliographic reference	Prandoni et al (2004) Below-knee compression stockings to prevent the post-thrombotic syndrome. Ann Intern Med 141:249-256

1yr (N=89)	65	23	1	1yr (N=89)	43	42	4
2yrs (N=85)	62	22	1	2yrs (N=81)	39	38	4
3yrs (N=82)	68	14	0	3yrs (N=76)	40	33	3
4yrs (N=68)	57	10	1	4yrs (N=58)	25	30	3
5yrs (N=35)	31	4	0	5yrs (N=29)	14	14	1

Recurrent VTE;
Confirmed; N=12/90 (13.3%) intervention, N=13/90 (14.4%) control

Adverse effects;
N=5/90 withdrew due to intolerance to the stockings
N=1/90 withdrew due to difficulty of putting the stocking on

Adherence;
N=78/84 (92.9%), wore stockings for ≥80% of daytime hours

Co-interventions;
N=12/90 (13.3%) of the control group (most 12 to 18mmHg at the ankle) for periods ranging from 6weeks to 6months, self-prescription or prescription of the attending physicians

Source of funding	Grant from New Medical Service, Linea Flebologica Flebysan, Italy. Stockings supplied by manufacturer
Comments	Analysis ITT, those lost to follow-up or died were censored Assumed 2year rate of PTS of approx. 50% in controls, for power of 90%, significance 0.05, needed N=85 per group to detect a 50% risk reduction with compression stockings

Bibliographic reference	**Aschwanden et al (2008) Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. J Vasc Surg 47:1015-1021**
Study type	RCT (open-label, computer-generated randomisation list, allocation concealed and performed via a study nurse not involved in the trial) Single centre
Aim	Study aim; to consider the effect of stockings to prevent PTS
Patient characteristics	Consecutive patients referred for exclusion/confirmation of DVT to a single centre, June 1997 to June 2004 Inclusion criteria; - >18years - First or recurrent proximal DVT (thrombosis of the popliteal vein or more proximal) confirmed by duplex ultrasound imaging - Had completed ≥6months of heparin, oral anticoagulant and compression stockings Exclusion criteria; - Chronic venous insufficiency (C4 to C6, by CEAP classification – corresponding to skin changes ascribed to venous disease with or without active or healed ulcer) - Advanced malignancy or death anticipated to occur ≤2years, long-lasting immobilisation - Geographic inaccessibility, dementia, peripheral arterial disease, contradicting compression therapy, anticipated lack of compliance Baseline characteristics were considered to be similar for baseline characteristics except sex (intervention; male (N=54, 64.3%, female N=30 (35.7%); control male (N=45, 52.9%, female N=40 (47.1%)) and same-leg previous DVT (intervention; N=18 (21.4%); control N=13 (15.3%))
Number of Patients	N=169 randomised
Intervention	N=84 A ready-to-wear, flat-knitted, below knee stocking with an applied pressure at the ankle of 26.3 to 36.1mmHg (manufactures not specified) All had standard DVT therapy before screening for study inclusion, heparin followed by oral anticoagulant and compression stockings (ankle pressure 26.3 to36.1mmHg) for at least 6months , at 6months screened for study inclusion
Comparison	N=85

<table>
<tr><td>Bibliographic reference</td><td>Aschwanden et al (2008) Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. J Vasc Surg 47:1015-1021</td></tr>
<tr><td></td><td>No stocking

All had standard DVT therapy before screening for study inclusion, heparin followed by oral anticoagulant and compression stockings for at least 6months</td></tr>
<tr><td>Length of follow up</td><td>Intervention, mean length of follow-up 3.2years (range 2months to 6.8years)
Control, mean length of follow-up 2.9years (range 1.5months to 7.0years)
Follow-up every 3months in the first year then every 6months, until endpoint reached or end of follow-up</td></tr>
<tr><td>Location</td><td>Switzerland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Definition of PTS; considered symptomatic if at least 1 or the following 5, pain, heaviness, sensation of heat, tension, tiredness of the affected limb

Primary outcome;
- Occurrence of emerging post-thrombotic skin changes according to C4 or higher

Secondary outcomes;
- PTS-associated symptoms

Lost to follow-up; N=19 (22.6%) intervention, N=20 (23.5%) control
N=3 died in each group

Adherence;
Full – defined as patient acknowledged wearing the stockings for ≥6days/week
Partial – wearing for 4/5days/week
Nonadherence – wearing for <4days/week

Results;
Occurrence of emerging post-thrombotic skin changes according to C4 or higher;
<table>
<tr><td></td><td>Intervention N=84</td><td>Control N=85</td><td>HR (95%CI) (ITT)</td><td>HR (95%CI) (as-treated#)</td></tr>
<tr><td>Post-thrombotic skin changes</td><td>11 (13.1%)</td><td>17 (20.0%)</td><td>0.60 (0.28 to 1.28), p=0.19</td><td>0.65 (0.31 to 1.40), p=0.27</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Aschwanden et al (2008) Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. J Vasc Surg 47:1015-1021**

Post-thrombotic skin changes*	11 (13.1%)	17 (20.0%)	0.61 (0.28 to 1.31), p=0.20	0.65 (0.30 to 1.42), p=0.28

*adjusted for previous DVT, age and sex

#7patients had crossover from their assigned treatment, median crossover time intervention group 33months (range 3 to 56months), median crossover time control group 4months (range 3 to 7months)

Subgroup analysis;

Showed no effect for <65years/>65years; no previous DVT/previous DVT; no obstruction/obstruction

Gender; male HR (95%CI) 1.07 (0.42 to 2.73); female HR (95%CI) 0.11 0.02 to 0.91)

PTS-associated symptoms;

Follow-up visits – reported on ≥1 of the 5 PTS-associated symptoms at any follow-up visit;

- N=77/629, 12.2% intervention group
- N=93/563, 16.5% control group

Adherence;

- Non-adherence recorded at 8.4% of follow-up visits; male in 11%, female in 3.6%
- Modelling noncompliance as a function of gender male to female OR(95%CI) 4.1 (1.0 to 16.0), p=0.05

Source of funding	
Comments	Primary efficacy analysis used ITT There is little information about the incidence of PTS, assumed a 45% incidence in the control group over 3years, assumed 50% relative risk reduction and a dropout of 10%; 80% power, two-tailed significance of 0.05 – N=85 needed per treatment arm

Bibliographic reference	**Kahn et al (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. The Lancet 383:880-888**
Study type	RCT (randomised via web-based syndrome which ensured allocation concealment, stratified by centre and used varying block sizes of four and eight. Blinded; patients, health-care providers, study personnel and study statisticians) Multi-centre, placebo-controlled
Aim	Study aim; to establish whether elastic compression stockings prevent post-thrombotic syndrome after proximal DVT

Bibliographic reference	Kahn et al (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. The Lancet 383:880-888
Patient characteristics	June 2004 to February 2010, 24 centres in Canada and the USA Inclusion criteria; - First symptomatic proximal DVT, with or without concurrent distal DVT or PE (proximal DVT – DVT in popliteal or more proximal deep leg veins, objectively confirmed with ultrasound in the previous 14 days) Exclusion criteria; - Contraindication to the use of compression stockings (such as allergy, severe arterial claudication) - Expected lifespan <6months, geographical inaccessibility, unable to apply stockings - Received thrombolytic therapy for the initial treatment of acute DVT Baseline characteristics similar between 2 groups; age categories, gender, ethnic origin, BMI, time from DVT diagnosis to randomisation, characteristics of DVT, most proximal extent of DVT (iliac, common femoral, femoral, popliteal), Villalta score, concurrent PE< VT risk factors, DVT treatment
Number of Patients	
Intervention	N=409 (of initial 410, N=2 did not receive the intervention) Active 30-40mmHg graduated elastic compressions stockings, knee-length, applied within 2weeks of DVT diagnosis – to wear on affected leg from waking until retiring for 2years, encouraged to keep active (Sigvaris, St Laurent, QC, Canada) Both intervention and comparison were applied within 2weeks of DVT diagnosis, replaced every 6months or earlier if torn or leg size had changed
Comparison	N=394 (of initial 396, N=4 did not receive the intervention) Placebo graduated elastic compression stockings <5mmHg compression at the ankle – to wear on affected leg from waking until retiring for 2years, encouraged to keep active
Length of follow up	Follow-up visits; 1, 6, 12, 18 and 24months
Location	Canada, USA
Outcomes measures and effect size	Definition of PTS; diagnosed using Ginsberg's criteria of ipsilateral pain and swelling for ≥1month that are typical in character (worse at the end of the day or with prolonged sitting or standing) Primary outcome; in original protocol – proportion of those with PTS at 24months, changed to cumulative incidence of PTS (time to first event) from 6 to 24months to use all study data (did not affect sample size)

Bibliographic reference	Kahn et al (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. The Lancet 383:880-888

Secondary outcomes; cumulative incidence and severity of PTS with Villatta's scale that grades intensity of 5 patient-related symptoms and 6 physical signs; objectively confirmed recurrent venous thromboembolism, death, adverse events, venous valvular reflux, quality of life (SF-36 and venous-disease specific VEINES-QOL/Sym)

Pre-specified subgroups; age, sex, BMI, proximal extent of index DVT

Frequent users; used study stockings for ≥3days/week at ≥3 study visits, or at ≥2 visits if there were fewer than 5 visits

Results

(N=3 identified as ineligible soon after randomisation, excluded from further analysis – modified ITT)

Cumulative incidence of PTS; (Ginsberg's criteria)

PTS; N=44/409, 14.2% intervention; N=37/394, 12.7%, control

HR (95%CI); 1.13 (0.73 to 1.76)

Secondary outcomes;

	Intervention (N=409)	Control (N=394)	HR (95%CI)
Cumulative incidence of PTS events as assessed by Villalta's criteria	176/409, 52.6%	168/394, 52.3%	1.00 (0.81 to 1.24)
Ipsilateral leg ulcer	17, 4.2% (17 ulcers)	16, 4.1% (17 ulcers)	
Recurrent VTE	33, 8.1% (45 events; 36 DVT, 9 PE)	38, 9.6% (44 events; 32 DVT, 12 PE)	
Recurrent ipsilateral DVT	16, 3.9% (18 events)	17, 4.3% (17 events)	
Death *	36, 8.8%	36, 9.1%	

*no deaths in either group were judged by investigators to be definitely or probably due to PE, or judged to be attributable (primary or contributing cause) to PE

Self-reported stocking use;

Overall;

- 1month; 734/764 (96.1%) wearing stockings, of these 660/764 (86.4%) were wearing for ≥3days/week

Bibliographic reference	**Kahn et al (2014) Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. The Lancet 383:880-888**

- 24months; 378/547 (69.1%) wearing stockings, of these 304/547 (55.6%) were wearing for ≥3days/week

	Intervention (N=409)				Placebo (N=394)			
	N completing the use form	Any use N (%)	Use ≥3days/wk	Hrs of use/day mean (SD)	N completing the use form	Any use N (%)	Use ≥3days/wk	Hrs of use/day mean (SD)
1mth	388/388	374 (96.4)	325 (83.8)	10.6 (4.2)	376/378	360 (95.7)	335 (89.1)	11.7 (3.7)
6mths	356/356	300 (84.3)	258 (72.5)	11.4 (3.3)	337/338	281 (83.1)	246 (72.8)	11.5 (3.3)
12mths	311/312	245 (78.8)	208 (66.9)	11.2 (3.6)	298/299	248 (83.2)	218 (73.2)	11.6 (3.3)
18mths	271/274	205 (75.6)	170 (62.7)	11.1 (3.6)	279/279	214 (76.7)	181 (64.9)	11.3 (3.3)
24mths	287/282	192 (69.1)	156 (56.1)	10.9 (3.1)	269/270	186 (68.9)	148 (54.8)	11.1 (3.5)

Adverse events;

- No serious AEs attributable to stockings in either group
- Minor AEs (rash, itching) N=8 (intervention), N=7 (placebo)

Source of funding	Grant from the Canadian Institutes of Health Research, active and placebo stockings provided as in-kind support by Sigvaris Corp Sponsor of the study stated to have had no role in study design, data collection, data analysis, data interpretation or writing of the report
Comments	Primary analysis compared in a modified ITT analysis with Cox regression adjusted for centre, loss to follow-up, withdrawals and death censored as of last date of follow-up Estimated cumulative incidence of primary outcome of 30% in placebo and 20% in intervention group over the 2year follow-up, i.e. a risk reduction of 33%. Total sample size needed for 0.05 and 80% was 800 (included adjustment for a projected 25% rate of loss to follow-up)

Appendix H: GRADE profiles

H.1 Review question 1: Thrombolysis for PE

Table 15: Thrombolysis compared with standard anticoagulation for patients with confirmed pulmonary embolism and haemodynamic stability who present with right ventricular dysfunction

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome 1: All-cause mortality - Figure 1											
7[1]	RCT	Serious[2]	Serious[3]	No serious	Serious[4]	No serious	18/813 (2.2%)	31/828 (3.7%)	0.68 (0.38 to 1.21)	12 fewer per 1000 (from 23 fewer to 8 more)	VERY LOW
Outcome 2: VTE-related mortality – Figure 2											
6[5]	RCT	Serious [6]	Serious[7]	No serious	Very serious[8]	No serious	3/752 (0.4%)	11/768 (1.4%)	0.42 (0.13 to 1.28)	8 fewer per 1000 (from 12 fewer to 4 more)	VERY LOW
Outcome 3: All major bleeding (including intracranial haemorrhage) – (i) sensitivity analysis (excluding Konstantinides 2002) - Figure 4											
5[9]	RCT	Serious[10]	Serious[11]	No serious	No serious	No serious	47/672 (7.0%)	9/667 (1.35%)	4.75 (2.37 to 9.54)	51 more per 1000 (from 18 more to 115 more)	LOW
Outcome 3a: Major bleeding: intracranial haemorrhage only - Figure 5											
6[12]	RCT	Serious[13]	Serious[3]	No serious	No serious	No serious	12/790 (1.5%)	1/805 (0.12%)	5.91 (1.30 to 26.83)	6 more per 1000 (from 0.4 more to 32 more)	LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome 3b: Major bleeding excluding intracranial haemorrhage – (i) sensitivity analysis (excluding Konstantinides 2002) - Figure 7											
5[9]	RCT	Serious[10]	Serious[11]	No serious	No serious	No serious	35/672 (5.21%)	8/667 (1.2%)	4.13 (1.90 to 8.99)	38 more per 1000 (from 11 more to 96 more)	LOW
Outcome 4: Composite all-cause mortality OR clinical deterioration / escalation of treatment - Figure 8											
4[14]	RCT	Serious[15]	Serious[16]	No serious	No serious	No serious	27/692 (3.9%)	67/710 (9.4%)	0.44 (0.29 to 0.67)	53 fewer per 1000 (from 31 fewer to 67 fewer)	LOW
Outcome 4a: Clinical deterioration / escalation of treatment (without mortality) component of composite outcome - Figure 9											
4[14]	RCT	Serious[15]	Serious[16]	No serious	No serious	No serious	16/692 (2.3%)	53/710 (7.5%)	0.34 (0.20 to 0.58)	49 fewer per 1000 (from 31 fewer to 60 fewer)	LOW
Outcome 4b: Mortality component of composite outcome - Figure 10											
4[14]	RCT	Serious[15]	Serious[16]	No serious	Very serious[24]	No serious	11/692 (1.6%)	14/710 (2.0%)	0.84 (0.38 to 1.83)	3 fewer per 1000 (from 12 fewer to 16 more)	VERY LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome 5: PE recurrence (non-fatal) – Figure 11											
7[1]	RCT	Serious[2]	Serious[3]	No serious	Very serious[8]	No serious	7/813 (0.86%)	17/828 (2.1%)	0.56 (0.24 to 1.30)	9 fewer per 1000 (from 16 fewer to 6 more)	VERY LOW
Outcome 6: Chronic thromboembolic pulmonary hypertension (CTEPH) – Figure 12											
2[17]	RCT	No serious	Very serious[18]	No serious	No serious	No serious	13/95 (13.7%)	40/95 (42.1%)	0.32 (0.18 to 0.57)	286 fewer per 1000 (from 181 fewer to 345 fewer)	LOW
Outcome 7: Quality of life at 3 months[19] (SF-36 Physical Component summary score <30; scale scored 0-100, lower score indicates poorer functioning) - Figure 13											
Kline 2014	RCT	No serious	Serious[20]	n/a	Serious[4]	No serious	1/37 (2.7%)	10/39 (25.6%)	0.11 (0.01 to 0.78)	228 fewer per 1000 (from 56 fewer to 254 fewer)	LOW

1. *Goldhaber 1993, Konstantinides 2002, Becattini 2010, Fasullo 2011, Sharifi 2013, Meyer 2014, Kline 2014*
2. *Outcome based on non-randomised subgroup analysis in 1 study (Goldhaber 1993); 2 studies were open label (Goldhaber 1993, Sharifi 2012); significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 3 studies (Konstantinides 2002, Meyer 2014, Kline 2014)*
3. *2 studies included patients not meeting review protocol criteria for objective evidence of RVD (Konstantinides 2002, Sharifi 2013)*
4. *The 95% CI is wide and crosses one MID so leading to some uncertainty in the result – downgrade 1 level*
5. *Goldhaber 1993, Konstantinides 2002, Becattini 2010, Fasullo 2011, Meyer 2014, Kline 2014*
6. *Outcome based on non-randomised subgroup analysis in 1 study (Goldhaber 1993); 1 study was open label (Goldhaber 1993); significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 3 studies (Konstantinides 2002, Meyer 2014, Kline 2014)*
7. *1 study, which has greatest weight in the meta-analysis, included patients not meeting review protocol criteria for objective evidence of RVD (Konstantinides 2002)*
8. *The 95%CI is wide, crossing both MIDs, so leading to significant uncertainty in the result – downgrade 2 levels*
9. *Becattini 2010, Fasullo 2011, Sharifi 2013, Meyer 2014, Kline 2014*
10. *I study was open label (Sharifi 2013); significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 2 studies (Meyer 2014, Kline 2014)*
11. *Sharifi (2013) included patients not meeting review protocol criteria for objective evidence of RVD*
12. *Konstantinides 2002, Becattini 2010, Fasullo 2011, Sharifi 2013, Meyer 2014, Kline 2014*
13. *One study was open label (Sharifi 2012); significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 3 studies (Konstantinides 2002, Mayer 2014, Kline 2014)*
14. *Konstantinides 2002, Becattini 2010, Meyer 2014, Kline 2014*

15. *Significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 3 studies (Konstantinides 2002, Meyer 2014, Kline 2014)*
16. *One study (accounting for >50% weight in the meta-analysis) included patients not meeting review protocol criteria for objective evidence of RVD (Konstantinides 2002)*
17. *Sharifi 2013, Kline 2014*
18. *1 study included patients not meeting review protocol criteria for objective evidence of RVD (Sharifi 2013); measures are proxy indicators of CTEPH*
19. *Denominator is all patients still alive at 3 months*
20. *SF-36 Physical Functioning scale is not a full and direct measure of quality of life after PE*

Table 16: Subgroup analyses: (a) by thrombolytic agent; (b) by age[1] – all studies

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Subgroup analysis 1a: Outcome: All-cause mortality by thrombolytic agent - Figure 14 Test for subgroup differences p=0.54											
(a) Tenecteplase											
3[2]	RCT	Serious[3]	No serious	No serious	Very serious[4]	No serious	13/574 (2.3%)	18/572 (3.1%)	0.73 (0.36 to 1.47)	8 fewer per 1000 (from 20 fewer to 15 more)	VERY LOW
(b) Alteplase											
4[5]	RCT	Serious[6]	Serious[7]	No serious	Very serious[4]	No serious	5/239 (2.1%)	13/256 (5.1%)	0.45 (0.12 to 1.76)	28 fewer per 1000 (from 45 fewer to 39 more)	VERY LOW
Subgroup analysis 1b: Outcome: All-cause mortality by mean age of study participants - Figure 15 Test for subgroup differences p=0.74											
(a) Mean age <65 years											
5[8]	RCT	Serious[9]	Serious[7]	No serious	Very serious[4]	No serious	6/279 (2.2%)	14/299 (4.7%)	0.57 (0.19 to 1.69)	20 fewer per 1000 (from 38 fewer to 32 more)	VERY LOW
(b) Mean age ≥65 years											
2[10]	RCT	Serious[11]	No serious	No serious	Very serious[4]	No serious	12/534 (2.2%)	17/529 (3.2%)	0.71 (0.35 to 1.46)	9 fewer per 1000 (from 21 fewer to 15 more)	VERY LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Subgroup analysis 2a: Outcome: All major bleeding (including intracranial haemorrhage) - Figure 16 Test for subgroup differences p=0.06											
(a) Tenecteplase											
3[2]	RCT	Serious[3]	No serious	No serious	No serious	No serious	45/574 (7.8%)	8/572 (1.4%)	5.19 (2.51 to 10.77)	59 more per 1000 (from 21 more to 137 more)	MOD
(b) Alteplase											
3[12]	RCT	Serious[13]	Serious[7]	No serious	Very serious[4]	No serious	3/216 (1.4%)	6/233 (2.6%)	0.63 (0.08 to 4.89)	10 fewer per 1000 (from 24 fewer to 100 more)	VERY LOW
Subgroup analysis 2b: Outcome: All major bleeding (including intracranial haemorrhage) – Figure 17 Test for subgroup differences p=0.05											
(a) Mean age <65 years											
4[14]	RCT	Serious[15]	Serious[7]	No serious	Very serious[4]	No serious	4/256 (1.6%)	6/276 (2.2%)	0.89 (0.18 to 4.49)	2 fewer per 1000 (from 18 fewer to 76 more)	VERY LOW
(b) Mean age ≥65 years											
2[10]	RCT	Serious[11]	No serious	No serious	No serious	No serious	44/534 (8.2%)	8/529 (1.5%)	5.33 (2.52 to 11.28)	65 more per 1000 (from 23 more to 155 more)	MOD

1 *The age subgroup analyses are at overall risk of bias due to the fact that subgroups are based on mean age of study participants and that all studies with mean ≥65yrs used tenecteplase while 4 of the 5 studies with mean age <65yrs used alteplase*
2 *Becattini 2010, Meyer 2014, Kline 2014*
3 *Significant differences at baseline in 2 studies (Becattini 2010, Meyer 2014); unblinding of treatment allocation occurred in 2 studies (Meyer 2014, Kline 2014)*
4 *The 95%CI is wide, crossing the MID in both directions so leading to significant uncertainty in the result – downgrade 2 levels*
5 *Goldhaber 1993, Konstantinides 2002, Fasullo 2011, Sharifi 2013*
6 *Outcome based on non-randomised subgroup analysis in 1 study (Goldhaber 1993); 2 studies were open label (Goldhaber 1993, Sharifi 2013);unblinding of treatment allocation occurred in Konstantinides 2002*
7 *2 studies included patients not meeting review protocol criteria for objective evidence of RVD (Konstantinides 2002, Sharifi 2013)*

[8] *Goldhaber 1993, Konstantinides 2002, Fasullo 2011, Sharifi 2013, Kline 2014*
[9] *Outcome based on non-randomised subgroup analysis in 1 study (Goldhaber 1993); 2 studies were open label (Goldhaber 1993, Sharifi 2013); unblinding of treatment allocation occurred in 2 studies (Konstantinides 2002, Kline 2014)*
[10] *Becattini 2010, Meyer 2014*
[11] *Significant differences at baseline in both studies; unblinding of treatment allocation occurred in Meyer (2014)*
[12] *Konstantinides 2002; Fasulo 2011; Sharifi 2013*
[13] *Unblinding of treatment allocation occurred in Konstantinides (2002); Sharifi (2013) was open label*
[14] *Konstantinides 2002; Fasulo 2011; Sharifi 2013; Kline 2014*
[15] *Sharifi (2013) was open label; unblinding of treatment allocation occurred in 2 studies (Konstantinides 2002, Kline 2014)*

Table 17: Within trial pre-specified subgroup analysis: by age (PEITHO trial, Meyer 2014)

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Subgroup analysis 1: Outcome: Death or Haemodynamic decompensation by age group - Figure 18 Test for subgroup differences p=0.34											
(a) ≤75 yrs											
Meyer 2014	RCT	Serious[1]	No serious	n/a	Serious[2]	No serious	6/344 (1.7%)	17/335 (5.1%)	0.34 (0.14 to 0.86)	33 fewer per 1000 (from 7 fewer to 44 fewer)	LOW
(b) >75yrs											
Meyer 2014	RCT	Serious[1]	No serious	n/a	Very serious[3]	No serious	7/162 (4.3%)	11/164 (6.7%)	0.64 (0.26 to 1.62)	24 fewer per 1000 (from 50 fewer to 42 more)	VERY LOW
Subgroup analysis 2: Outcome: Major extracranial bleeding - Figure 19 Test for subgroup differences p=0.10											
(a) ≤75 yrs											
Meyer 2014	RCT	Serious[4]	No serious	n/a	Serious[2]	No serious	14/344 (4.1%)	5/335 (1.5%)	2.73 (0.99 to 7.49)	26 more per 1000 (from 0 fewer to 97 more)	LOW
(b) >75yrs											
Meyer 2014	RCT	Serious[4]	No serious	n/a	No serious	No serious	18/162 (11.1%)	1/164 (0.6%)	18.22 (2.46 to 134.91)	105 more per 1000 (from 9 more to 817 more)	MOD

1 *Significant differences at baseline on two clinical characteristics that may affect outcome*
2 *The 95% CI is wide and crosses one MID, so leading to some uncertainty in the result – downgrade 1 level*
3 *The 95%CI is wide, crossing the MID in both directions so leading to significant uncertainty in the result – downgrade 2 levels*
4 *Significant differences at baseline on two clinical characteristics that may affect outcome; unblinding of treatment allocation occurred in a small proportion of patients*

H.2 Review question 2: Compression stockings for PTS prevention

Quality assessment							No of patients		Effect estimate	
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative risk (95% CI)	Quality
Outcome: post thrombotic syndrome - Figure 20										
3a	RCT	Serious[1]	Serious[2]	Serious[3]	Serious[4]	No serious	97/592	150/582	0.64 (0.37 to 1.12)	Very low
Outcome: recurrence of VTE - Figure 21										
3a	RCT	Serious[1]	Serious[2]	Serious[3]	Serious[4]	No serious	59/595	64/582	0.91 (0.65 to 1.27)	Very low
Outcome: adherence/compliance										
Brandjes 1997	RCT	Very serious[5,6]	Serious[7]	N/A	N/A	No serious	N=16/96 usually wore N=73/96 always wore	N/A – no stockings as comparator	N/A	Very low
Prandoni 2004	RCT	Very serious[5,6]	Serious[7]	N/A	N/A	No serious	N=78/84 wore ≥80% daytime hours	N/A – no stockings as comparator	N/A	Very low
Kahn 2014	RCT	Very serious[6]	Serious[7]	N/A	N/A	No serious	At 1month; N=325/388 (83.8%) wearing for ≥3days/wk At 24months; N=156/287(56.1%) wearing	At 1month; N=335/376 (89.1%) wearing for ≥3days/wk At 24months; N=148/269(54.8%) wearing for ≥3days/wk	N/A	Very low

Quality assessment							No of patients		Effect estimate	
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative risk (95% CI)	Quality
							for ≥3days/wk			
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Treatment**	**Comparator**	**Relative risk (95% CI)**	
Aschwanden 2008	RCT	Very serious[5,6]	Serious[8]	N/A	N/A	No serious	Non adherence 8.4%	N/A	N/A	Very low
Outcome: adverse skin events (venous ulceration)										
Brandjes 1997	RCT	Very serious[5, 6]	Serious[11]	N/A	N/A	No serious	3/96	1/96	N/A	Very low
Outcome: adverse skin events (post-thrombotic skin changes)										
Aschwanden 2008	RCT	Very serious[9,10]	Serious[8]	N/A	N/A	No serious	N=11/84	N=17/84	HR 0.61 (0.28 to 1.31), p=0.20 (adjusted for previous DVT, age, sex)	Very low

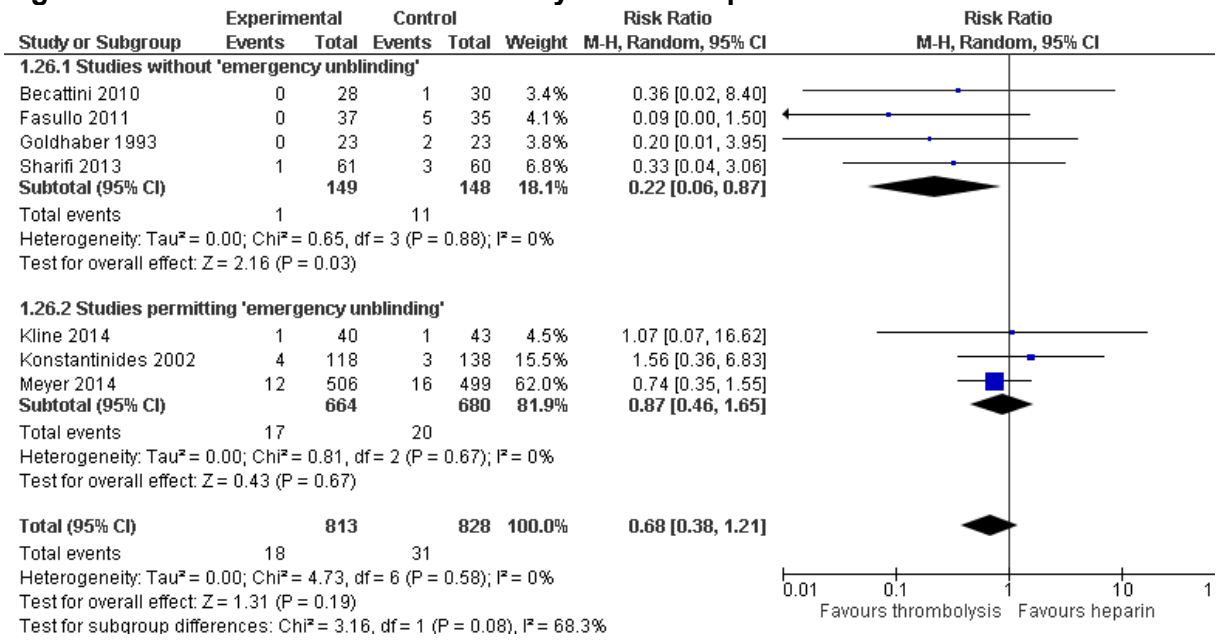
[a] *Brandjes (1997), Kahn (2014), Prandoni (2004)*

1 *2 out of 3 RCTs were single centre, open-label studies*
2 *Differences in the definitions of post-thrombotic syndrome used*
3 *2 out of 3 RCTs used no stocking as a control, 1 RCT used a placebo stocking, differing criteria used to defined PTS*
4 *CIs cross the MID (using default MID)*
5 *Open-label, single centre*
6 *Self-reported*
7 *Use of a compliance scale (no details on validation) or arbitrary decisions on what met the adherence/compliance criteria*
8 *Both groups had worn compression stockings as part of their initial 6months of treatment*
9 *Open-label, single centre*
10 *Self-reported*
11 *Unclear criteria for diagnosis*

Appendix I: Forest plots

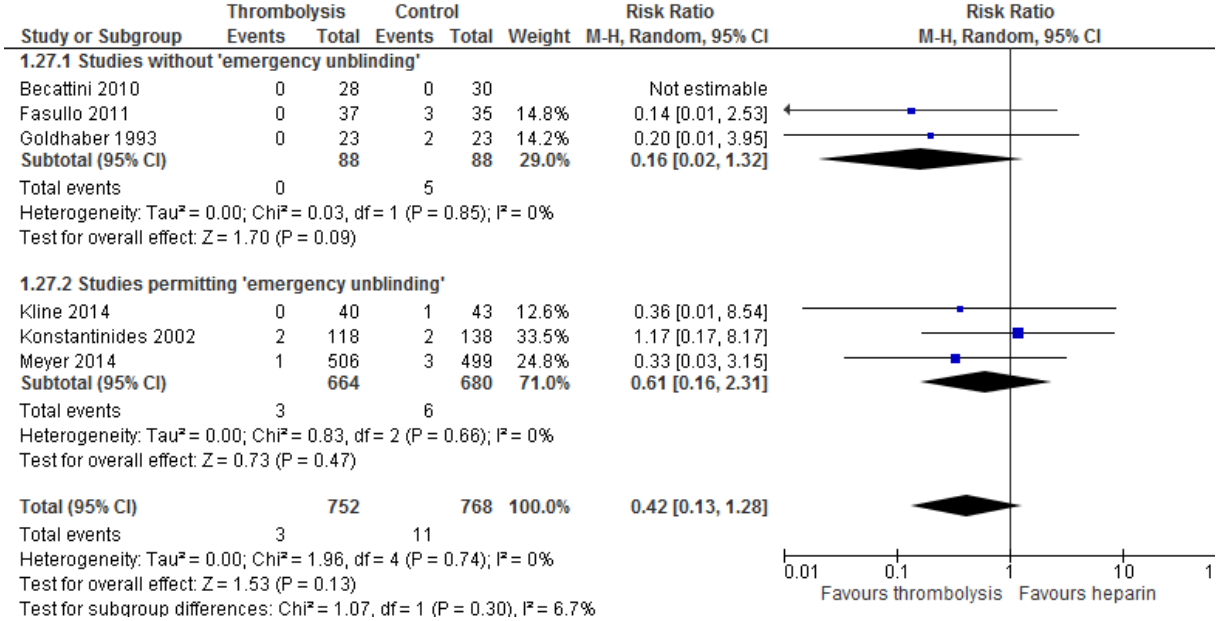
I.1 Review question 1: Thrombolysis for PE

Figure 1: Outcome 1: All-cause mortality[a] – GRADE profile: Table 15



[a] *Timepoints: Becattini (2010) 30d post-randomisation, Fasullo(2011) in hospital / first 10d; Goldhaber (1993) within 14d or in hospital, if longer; Sharifi (2013) 'in hospital'; Kline (2014) within 5d; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014) at 30d post-randomisation*

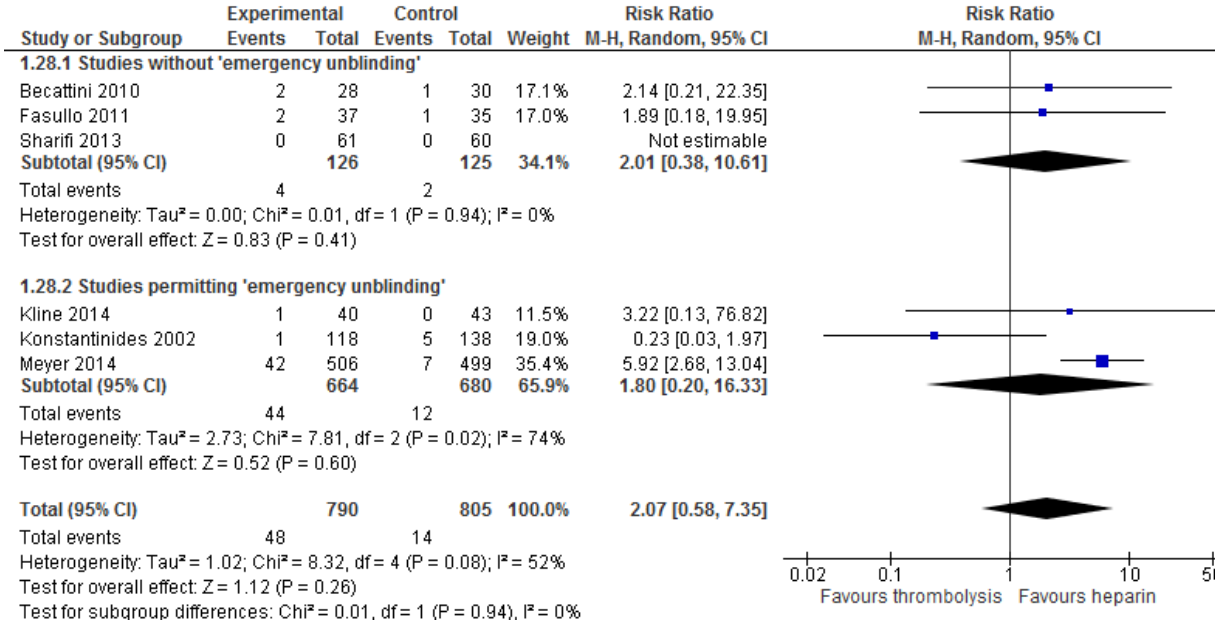
Figure 2: Outcome 2: VTE-related mortality[b] – GRADE profile: Table 15



[b] *Timepoints: Becattini (2010) 30d post-randomisation, Fasullo(2011) in hospital / first 10d; Goldhaber (1993) within 14d or in hospital, if longer; Kline (2014) within 5d; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014) at 30d post-randomisation*

Figure 3: Outcome 3: All major bleeding (including intracranial haemorrhage)[c]

No GRADE profile due to significant within-subgroup heterogeneity



[c] *Timepoints: Becattini (2010) 7d or discharge (whichever first), Fasullo (2011) in hospital / first 10d; Sharifi (2013) 'in hospital'; Kline (2014) within 5d; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014) within 7d*

Figure 4: Outcome 3a: Sensitivity analysis: All major bleeding (including intracranial haemorrhage) – excluding Konstantinides 2002 – GRADE profile: Table 15

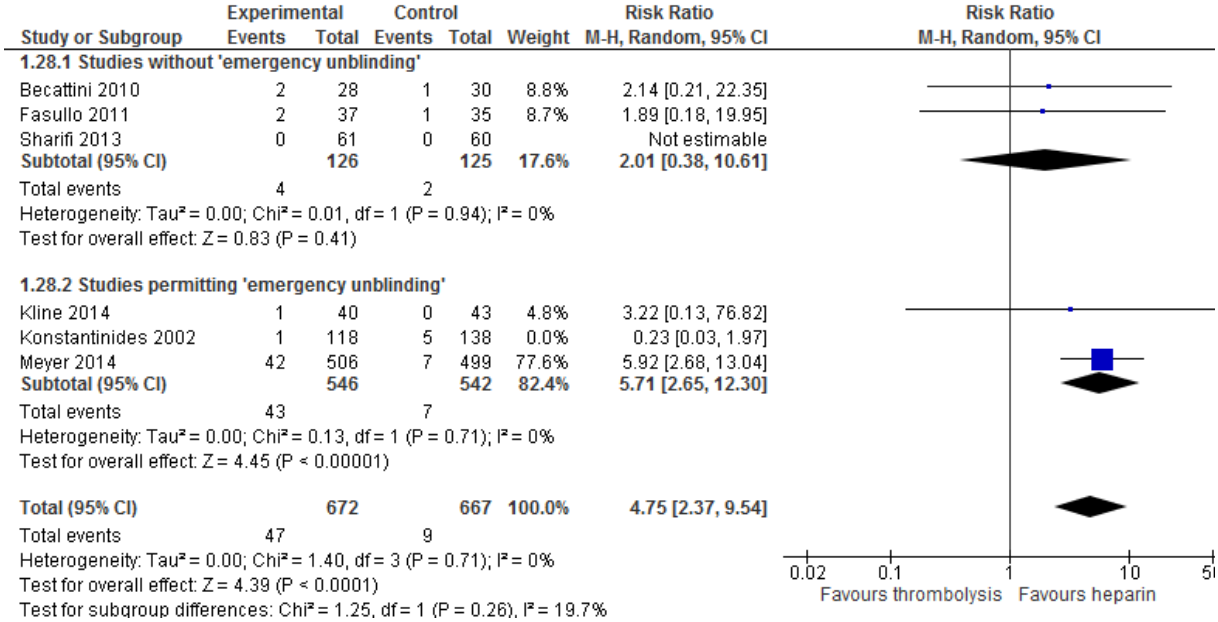
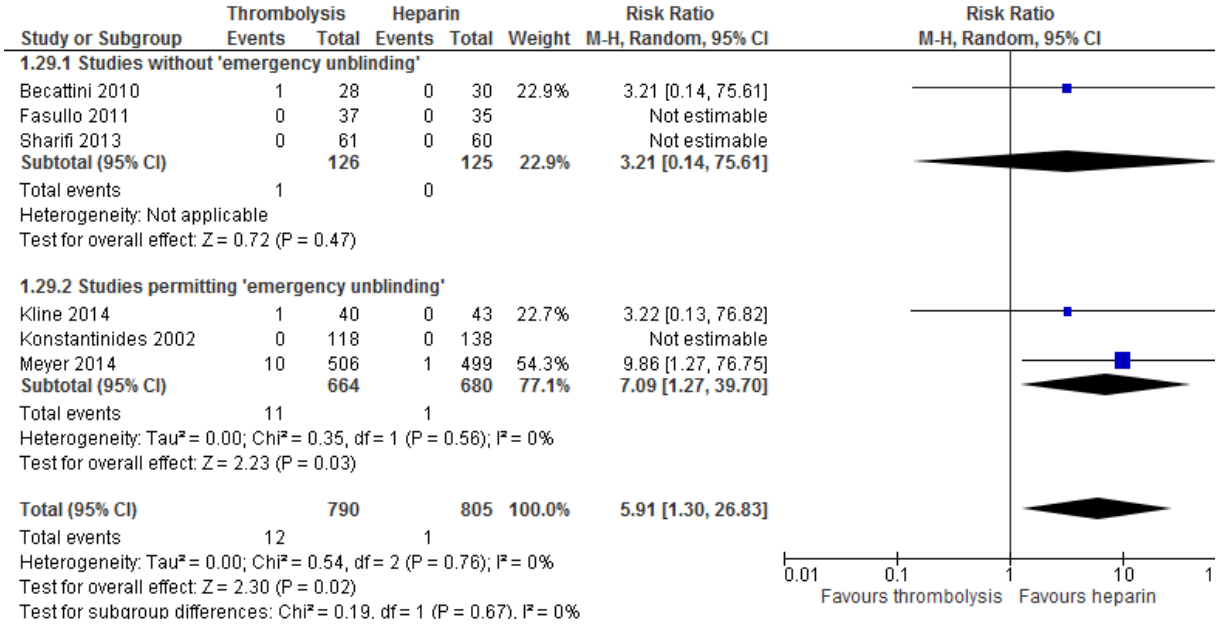


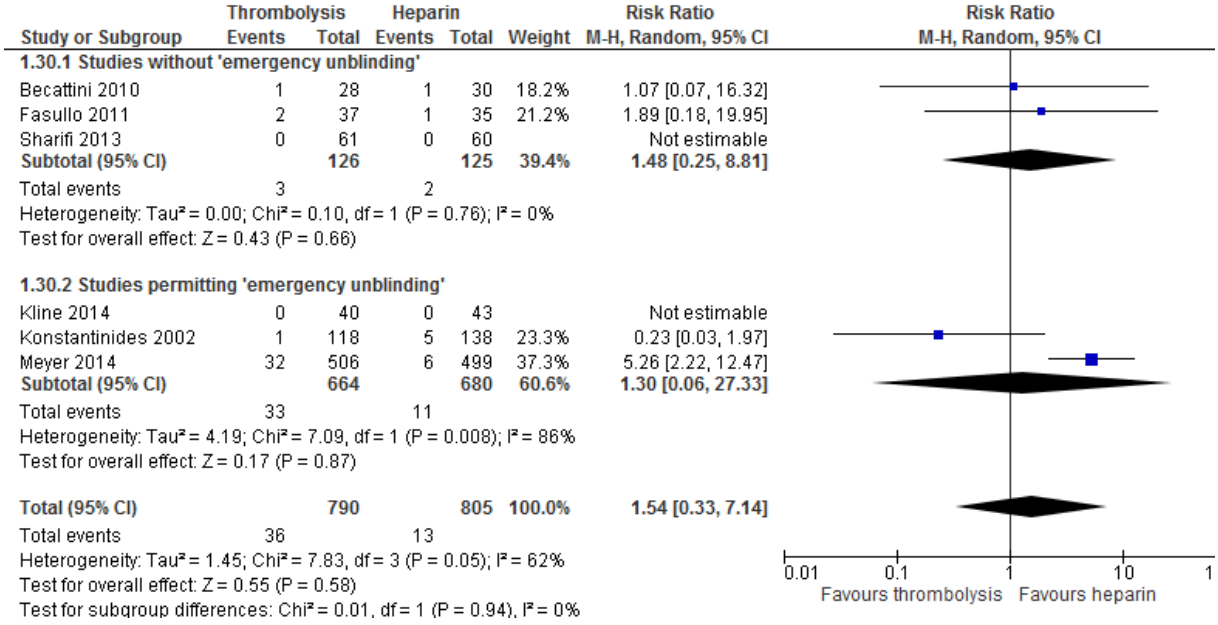
Figure 5: Outcome 3(i): Intracranial haemorrhage[d] – GRADE profile: Table 15



[d] *Timepoints: Becattini (2010) 7d or discharge (whichever first), Kline (2014) within 5d; Meyer (2014) within 7d*

Figure 6: Outcome 3(ii): Major bleeding excluding intracranial haemorrhage[e]

No GRADE profile due to significant within-subgroup heterogeneity



[e] *Timepoints: Becattini (2010) 7d or discharge (whichever first), Fasullo (2011) in hospital / first 10d; Sharifi (2013) 'in hospital'; Kline (2014) within 5d; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014) within 7d*

Figure 7: Outcome 3(ii)a: Sensitivity analysis: Major bleeding excluding intracranial haemorrhage – excluding Konstantinides 2002 – GRADE profile: Table 15

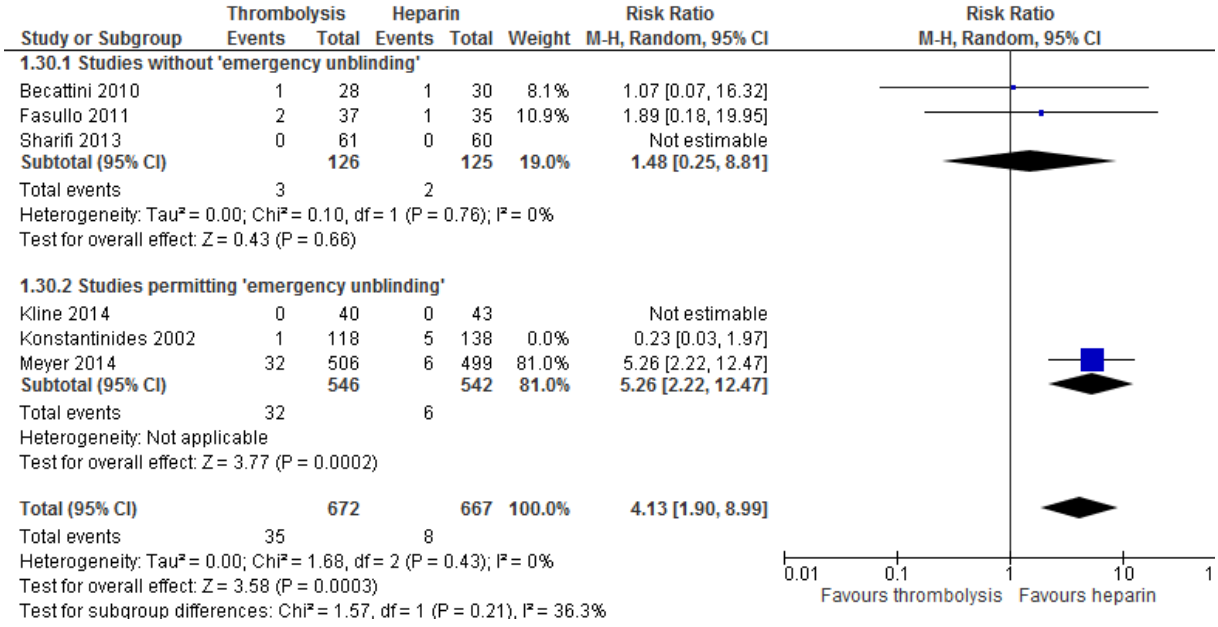
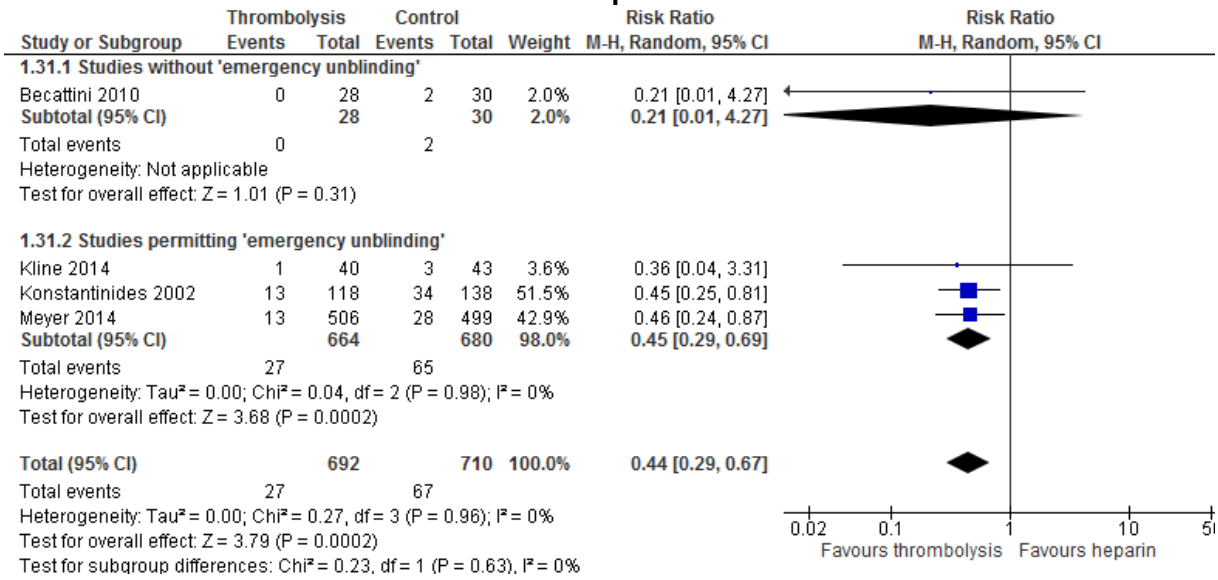


Figure 8: Outcome 4: Composite all-cause mortality OR clinical deterioration / escalation of treatment[f] – GRADE profile: Table 15



[f] *Timepoints: Becattini (2010) 7d; Kline (2014) 5d; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014)7d*

Figure 9: Outcome 4(i): Clinical deterioration component of composite outcome[f] – GRADE profile: Table 15

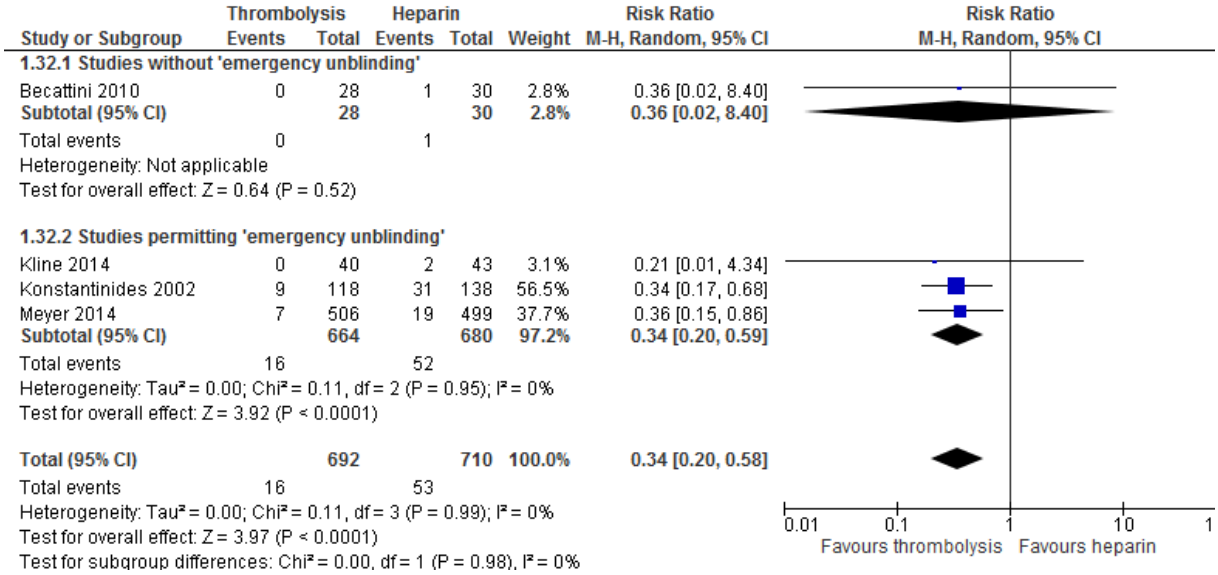


Figure 10: Outcome 4(ii): Mortality component of composite outcome – GRADE profile: Table 15

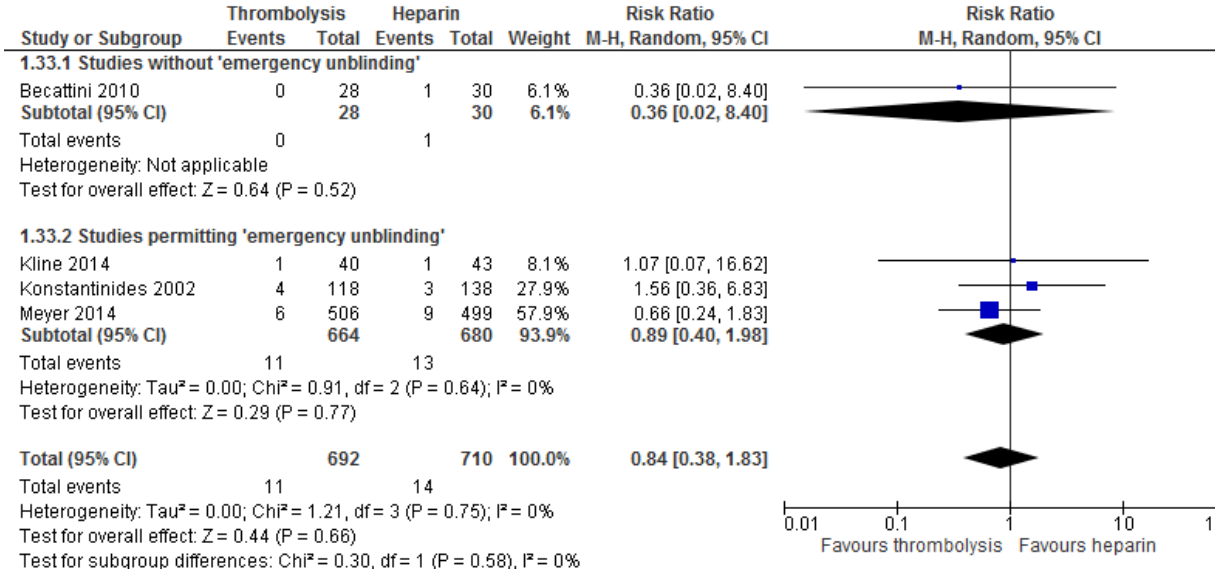
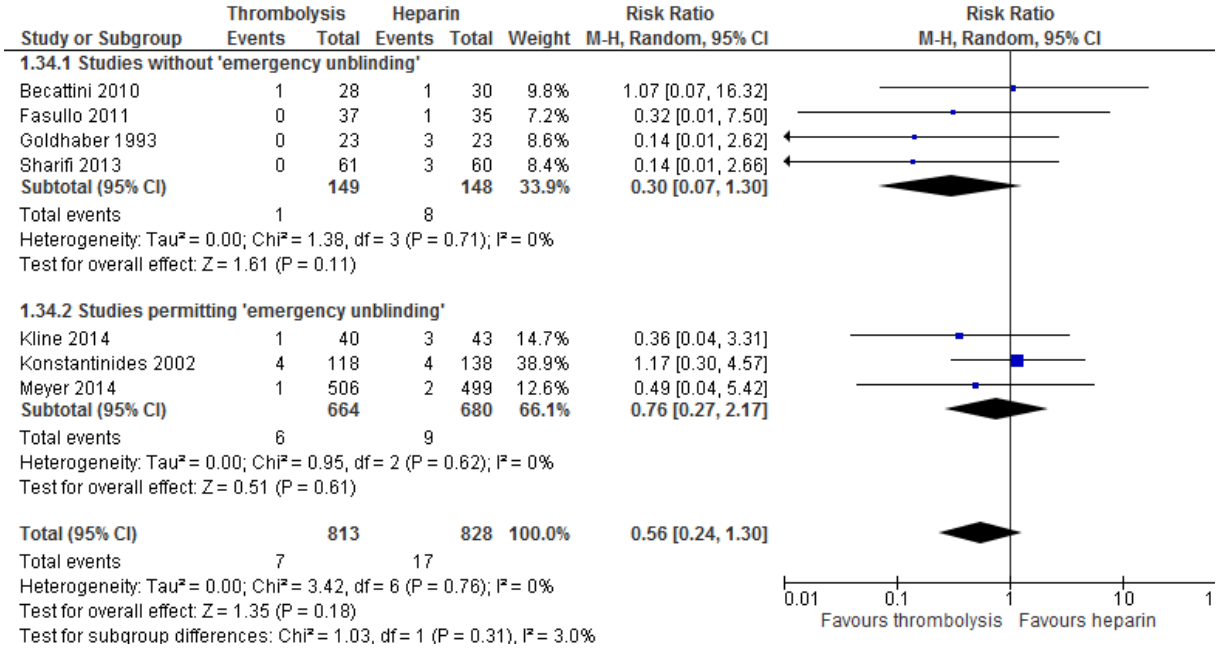
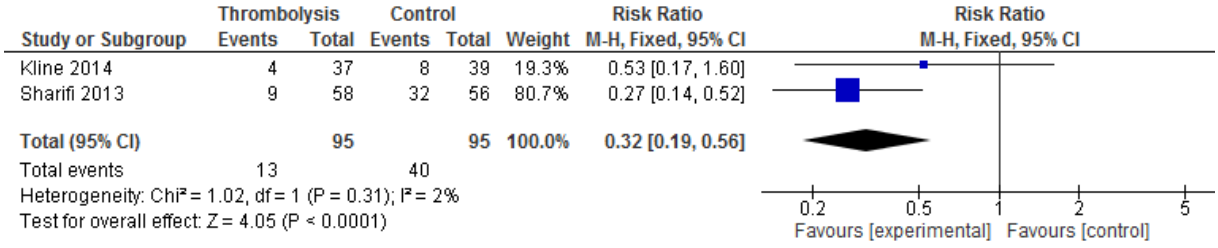


Figure 11: Outcome 5: PE recurrence (non-fatal)[g] – GRADE profile: Table 15



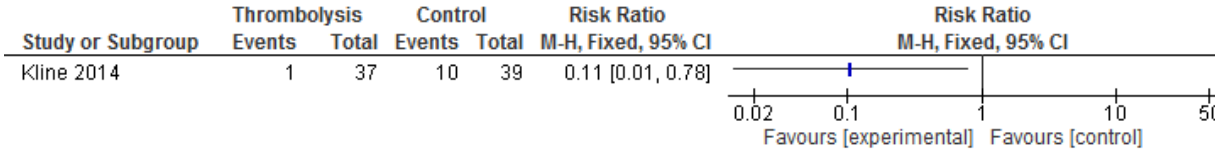
[g] *Timepoints: Becattini (2010) 7d or discharge (whichever first), Fasullo (2011) 6 months(cumulative in-hospital + follow up); Goldhaber (1993) within 14d or in hospital, if longer; Sharifi (2013) 'in hospital'; Kline (2014) 3 months; Konstantinides (2002)in hospital or within 30d (whichever first); Meyer (2014) within 7d*

Figure 12: Outcome 6: Proxy indicators of chronic thromboembolic pulmonary hypertension (CTEPH)[h] – GRADE profile: Table 15



[h] *Timepoints: Kline (2014) 3 months; Sharifi (2013) 28±6 months*

Figure 13: Outcome 7: Quality of life at 3 months (SF-36 Physical Component summary score <30)[i] – GRADE profile: Table 15



[i] *Scale scored 0-100; lower score indicates poorer functioning*

Subgroup analyses: (a) by thrombolytic agent; (b) by age – all studies

Figure 14: Subgroup analysis 1a: All-cause mortality by thrombolytic agent – GRADE profile: Table 16

(Test for subgroup difference p=0.54)

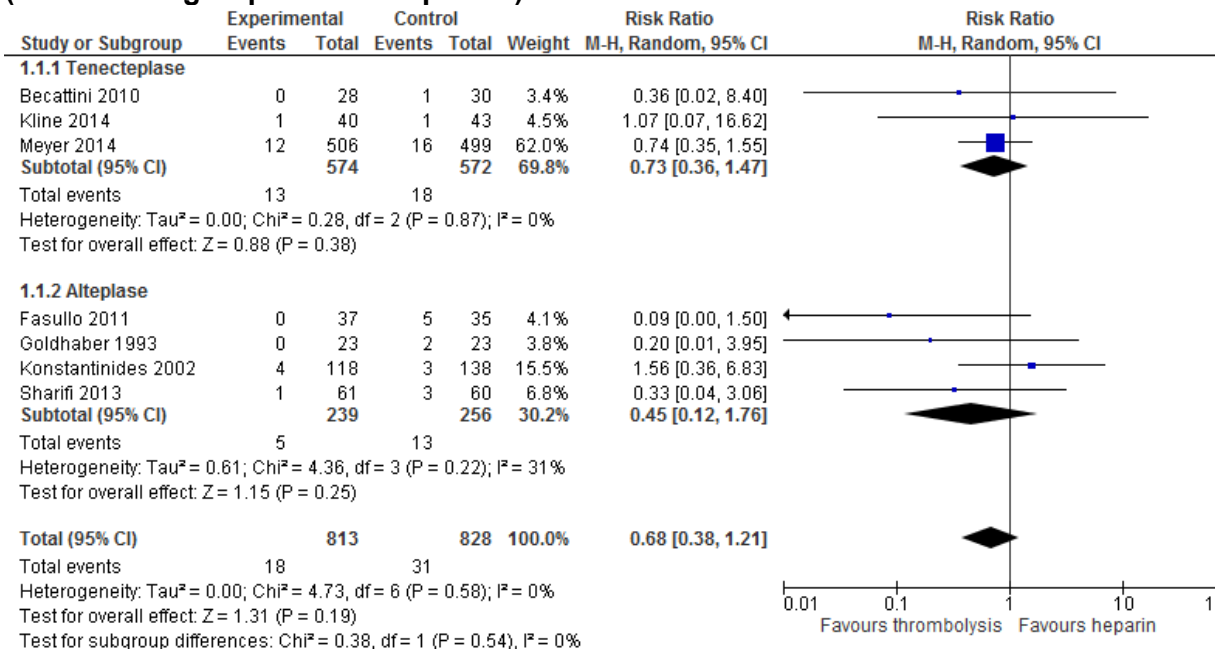


Figure 15: Subgroup analysis 1b: All-cause mortality by mean age of study participants – GRADE profile: Table 16

(Test for subgroup difference p=0.74)

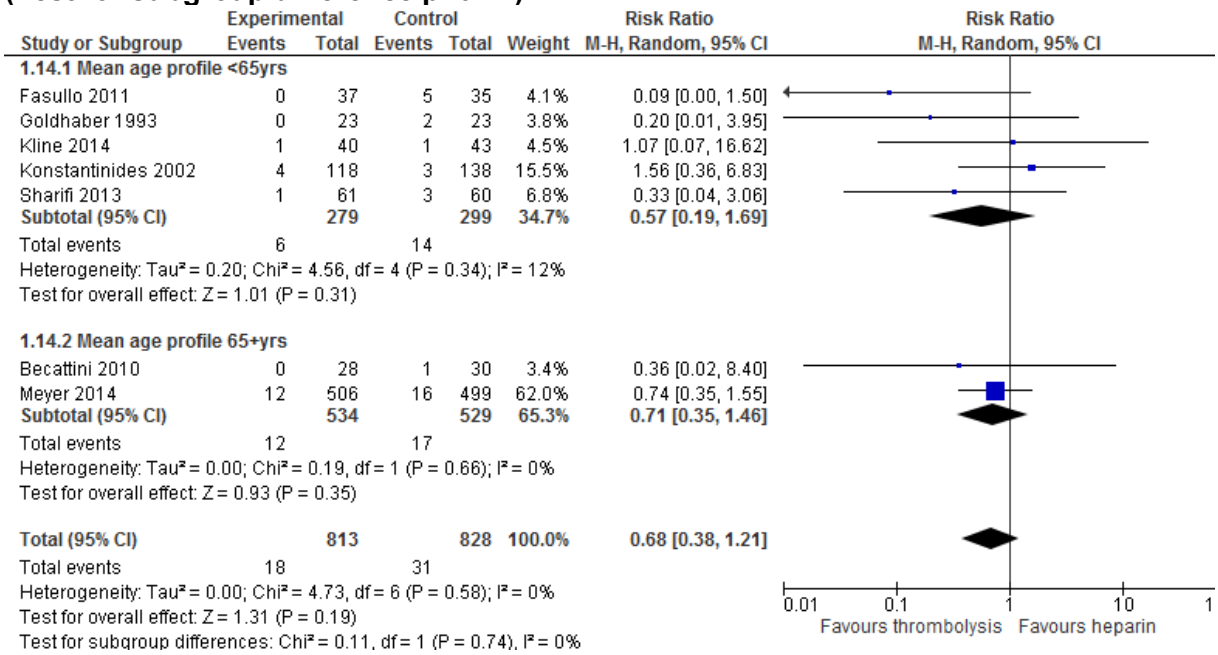


Figure 16: Subgroup analysis 2a: All major bleeding (including intracranial haemorrhage) – GRADE profile: Table 16

(Test for subgroup difference p=0.06)

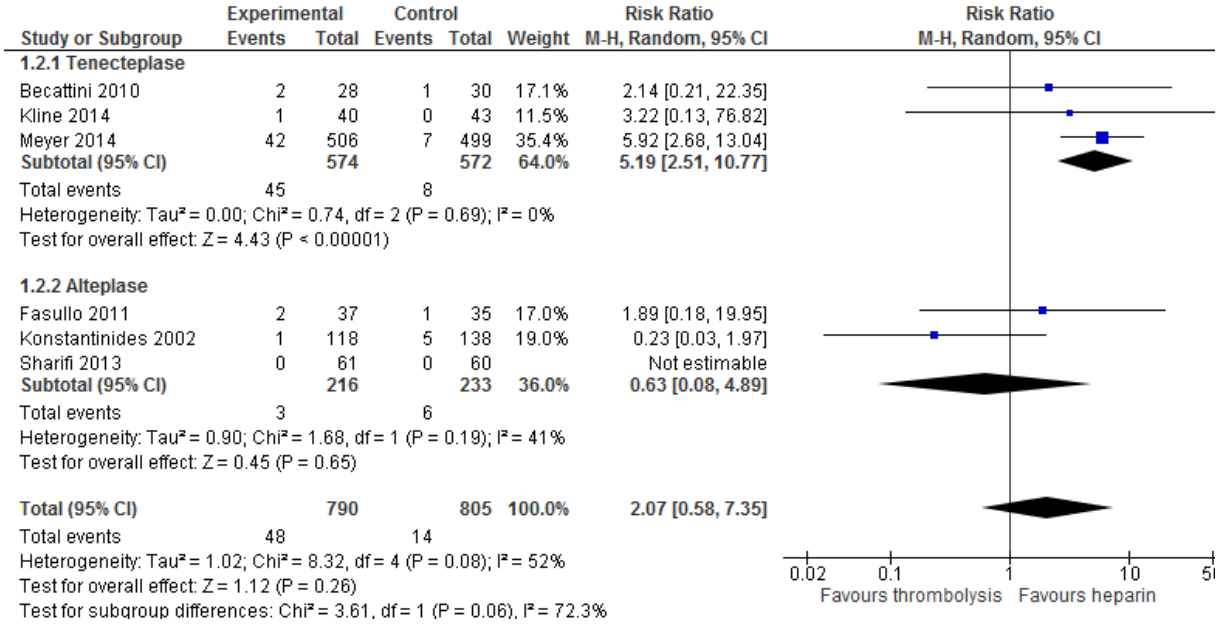
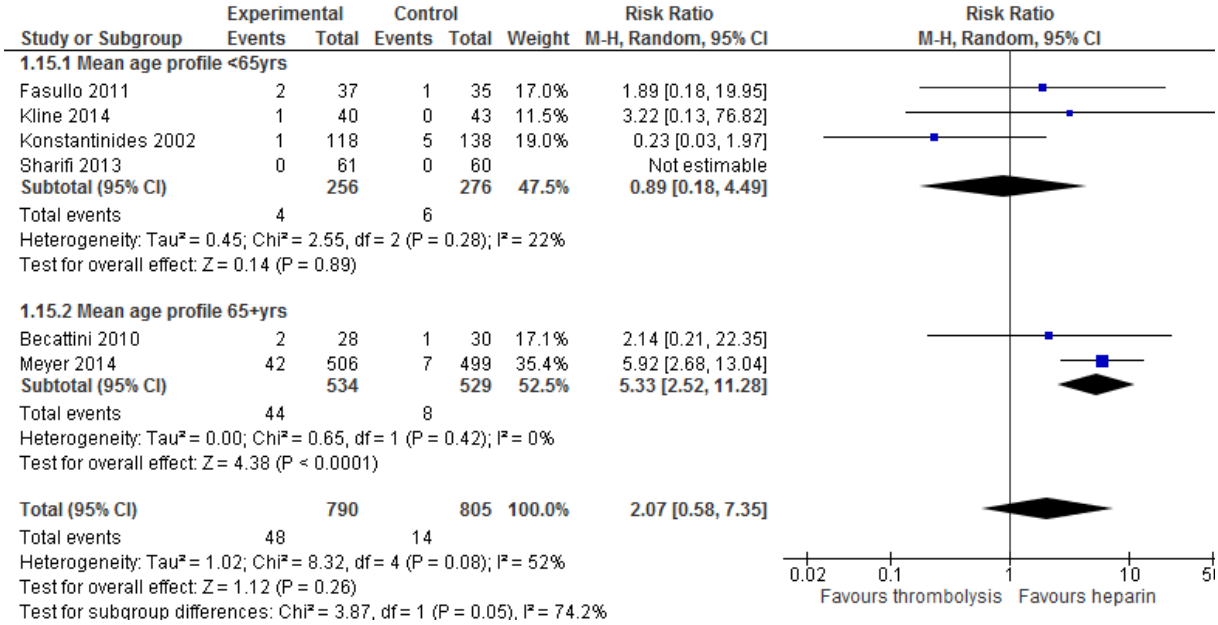


Figure 17: Subgroup analysis 2b: All major bleeding (including intracranial haemorrhage) – GRADE profile: Table 16

(Test for subgroup difference p=0.05)



Within trial pre-specified subgroup analysis: by age (PEITHO trial, Meyer 2014)

Figure 18: Subgroup analysis 1: Outcome: Death or Haemodynamic decompensation by age group – GRADE profile: Table 17

(Test for subgroup difference p=0.34)

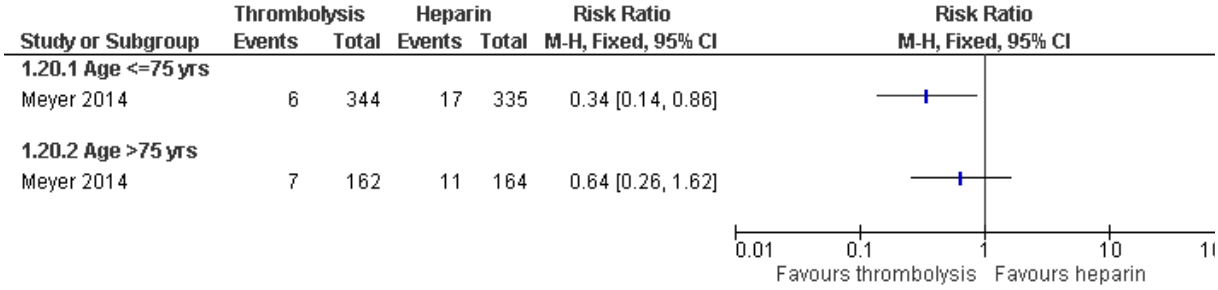
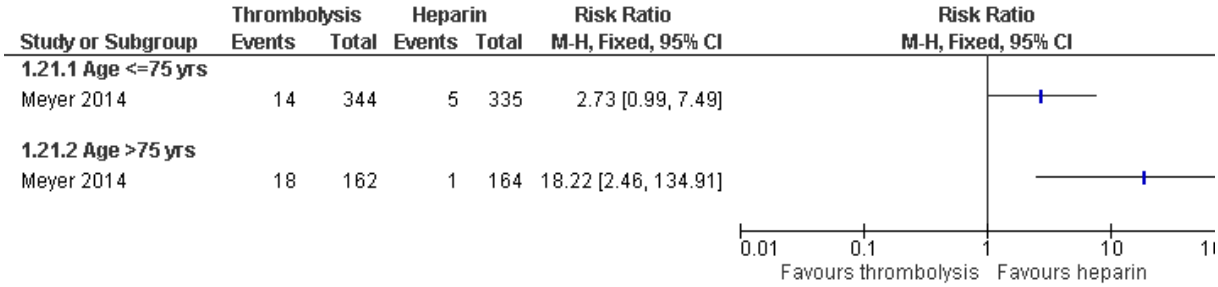


Figure 19: Subgroup analysis 2: Outcome: Major extracranial bleeding – GRADE profile: Table 17

(Test for subgroup difference p=0.10)



I.2 Review question 2: Compression stockings for PTS prevention

Figure 20: Post-thrombotic syndrome:

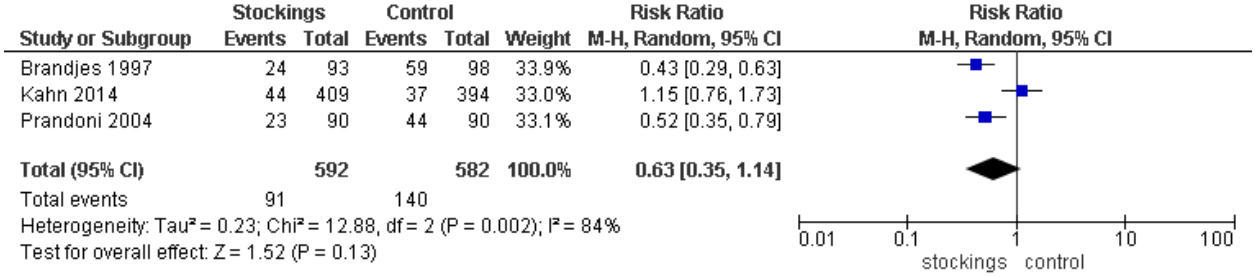


Figure 21: Recurrence of VTE: