National Institute for Health and Care Excellence

Draft for consultation

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

[E] Evidence review for outpatient treatment of low risk PE

NICE guideline

Evidence reviews

November 2019

Draft for Consultation

This evidence review was developed by the NICE Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Outpatient treatment of low-risk PE

Review question

What is the clinical and cost effectiveness of outpatient treatment for low risk suspected or confirmed PE?

Introduction

Pulmonary embolism (PE) is a potentially fatal disease associated with high morbidity. People with acute PE fall into high-risk[1] and low-risk[2] groups based on their haemodynamic status and the presence or absence of other factors such as new-onset arrhythmia, hypovolaemia, or sepsis. People with a PE having few clinical signs of haemodynamic compromise have a low risk of short-term mortality.

Historically, all people with confirmed PE have been treated as inpatients in a hospital environment, however, increasingly people are being discharged and treated as outpatients if they are haemodynamically stable. This avoids the risk of hospital-acquired morbidities and the stress and anxiety associated with being treated in hospital and may also reduce costs to the health service.

A number of tools have been developed to stratify PE risk, including the Pulmonary Embolism Severity Index (PESI), the simplified version of the PESI (sPESI) and Hestia criteria. These tools could be used to identify people with low-risk PE who could be treated on an outpatient basis.

The aim of this review is to determine whether people with low-risk PE could be given effective and safe treatment on an outpatient basis. It identified studies that fulfilled the conditions listed in Table 1. For full details of the review protocol, see appendix A.

PICO table

Table 1: PICO table for outpatient treatment in low-risk PE

Population	Adults (18+ years) with low-risk suspected or confirmed PE.
Intervention	Treatment for PE in outpatient settings.
Comparator	Treatment for PE in inpatient settings.

Outcomes	• All-cause mortality
	• VTE-related mortality
	• Recurrence of VTE (Split by recurrent DVT and recurrent PE if data is available)
	• Unplanned admission
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	• Adverse events
	  ○ Major bleeding
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.

[1] High-risk PE (massive PE), defined by the presence of shock or persistent arterial hypotension (systolic blood pressure < 90 mmHg or systolic blood pressure drop by ≥ 40 mm Hg, for > 15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis). Definition taken from Yoo et al (2019).

[2] Low-risk PE is defined as non-high risk PE (non-massive PE).

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix B.

This review was based in part on a Cochrane review (Yoo et al. 2019) of RCTs for inpatient versus outpatient treatment of VTE.

In addition, the following points apply:

1. The protocol for this review included both RCT and prospective observational studies because of the predicted low number of RCTs addressing this issue.
2. Based on the Cochrane review, outpatients were defined as people who were discharged within 36 hours after the low-risk acute PE diagnosis then completed treatment at home.
3. Inpatient settings were defined as settings where patients are admitted and provided with a bed for one or more nights.
4. Participants were considered low-risk if they were classified as low-risk by any validated or non-validated measurement tool that aimed to classify mortality risk rate related to PE (for example GPS, PESI, HESTIA).

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Clinical evidence

Included studies

The protocol for this review included both RCTs and prospective observational studies as evidence. The Cochrane vascular group update of the review 'Outpatient versus inpatient treatment for acute pulmonary embolism' by Yoo et al. 2019 was updated during the timeframe of this VTE guideline update and was directly relevant to this review question. This Cochrane review is an update of an earlier Cochrane review (Yoo et al. 2014), which identified a second study to the one included in the original review, leading to the inclusion of 2 randomised controlled trials.

An additional search was performed to identify any prospective observational studies to supplement the RCT evidence. Of the 4,894 studies identified, 4,867 were excluded at title and abstract screening stage because they did not match the review protocol, leaving 27 included studies for the full text screen. At the full text screening stage all studies were excluded leaving 0 included observational studies.

A second set of searches, using the original search strategies, were conducted at the end of the guideline development process to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened on title and abstract. Nine additional studies were identified at title and abstract screening, but no additional relevant references were included at full text screening for this review question.

The process of RCT and observational study identification is summarised in the PRISMA diagram in appendix D.

The references for the included studies are listed in appendix J.

Excluded studies

Details of the studies excluded at full text, with reasons for exclusion and full references are given in appendix I. Common reasons for exclusion were not reporting on PE population or not stratifying results between inpatient and outpatient groups.

Summary of clinical studies included in the evidence review

The Yoo (2019) review was judged to be high quality and partially applicable because it only included RCTs and the protocol for this review also included observational studies. As a result, it was used as a source of both relevant RCTs and data. Two studies were identified in the Yoo (2019) review. Both studies provided results for all-cause mortality, major bleeding, quality of life and PE recurrence. Peacock 2018 also presented results for minor bleeding and total serious adverse events.

Further study characteristics are presented in Table 2.

Table 2: Summary of characteristics of included RCTs

Author	Sample size	Outpatient treatment	Inpatient treatment	Study location
Aujesky 2011	339	Subcutaneous enoxaparin (Self/caregiver/visiting nurse administered) 1 mg/kg twice daily and discharged from the emergency dept. within 24 hours of randomisation + VKA.	Subcutaneous enoxaparin 1 mg/kg twice daily and admitted to hospital + VKA.	19 emergency departments in: • Switzerland, • France, • Belgium • United States
Peacock 2018	112	Rivaroxaban 15 mg orally twice daily for the first 21 days followed by 20 mg orally once daily for approximately 69 days for a total treatment duration of 90 days	Local standard-of-care as per local protocol and defined by the medical team caring for the participant, which typically involves bridging therapy and hospitalisation, but may also include any of the direct oral anticoagulants (DOACs).	35 sites in the United States

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

Risk of bias for the RCTs was assessed using the Cochrane risk of bias tool judgements reported in the original Cochrane review and reproduced in appendix E. The overall judgement of risk of bias for each study was determined by the Guideline Updates Team and the results are summarised in Table 5. For forest plots see appendix F and for GRADE tables please see appendix G. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

A systematic search was carried out for this review question to identify relevant economic analyses. The search returned 1,772 citations, all of which were excluded on title and abstract.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single re-run search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Therefore, no published cost-effectiveness studies were included in this review and this question was not prioritised for *de novo* economic modelling.

Evidence statements

The format of the evidence statements is explained in appendix B.

- High quality evidence from 2 RCTs with 444 people **found no meaningful difference** in patient satisfaction questionnaire scores between outpatient treatment and inpatient treatment of people with low-risk pulmonary embolism.
- Low to moderate quality evidence from up to 2 RCTs with up to 451 people **could not differentiate** short-term all-cause mortality, long-term all-cause mortality, major bleeding, minor bleeding, recurrent PE, or total serious adverse events in outpatient treatment compared to inpatient treatment of people with low-risk pulmonary embolism.

Economic evidence statements

No relevant economic evidence was identified for this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that their main aim is to ensure that the safety of people undergoing outpatient treatment for PE is not compromised compared to people undergoing inpatient treatment. As a result, they agreed that mortality and bleeding were key outcomes for this review question.

The quality of the evidence

The evidence for the outcomes in this review ranged from high to low quality. Both RCTs were judged to be at low risk of bias. However, the committee noted that there were no UK centres in either of the RCTs and that in Aujesky 2011, the enoxaparin dose did not reflect UK practice (1.5 mg/kg once daily). The committee decided that this evidence was still directly applicable to the review question.

No studies were identified that looked at people with suspected PE. In the absence of any data, the committee agreed that data for people with confirmed PE could be extrapolated to this population (see benefits and harms below.)

The committee noted that while Aujesky 2011 provided identical treatment regimens to both inpatients and outpatients, Peacock 2018 provided different treatment

regimens for inpatients and outpatients. Despite these differences the committee agreed that the studies could be included in the same meta-analysis with subgroup analyses, to look at these studies separately. However, it was not possible to examine subgroup differences for most outcomes of interest due to there being zero events in one or more studies. The inpatient treatment in Peacock 2018 was also subject to treatment variation, as standard of care was delivered per local protocol, meaning that different people in the inpatient group could receive different treatments. In addition, the committee noted that the 2 trials used different anticoagulant treatments: Peacock 2018 used rivaroxaban, an oral treatment, whilst Aujesky 2011 used enoxaparin, a subcutaneous anticoagulant injection, and this could lead to differences in adherence between the two trials.

These studies also used different validated tools to stratify risk. Aujesky 2011 used PESI scoring, in which people are given a risk score of 1 to 5 based on 11 different factors including age, sex, past medical history, comorbidities and clinical symptoms. People with a PESI I or PESI II score are classified as low-risk. Peacock 2018 used the Hestia exclusion criteria to stratify risk. If a person with PE has any of the 11 Hestia exclusion criteria, they are classified as “not-low” risk. The committee commented that the Hestia criteria might be easier to use to screen people with PE for outpatient treatment as people are either scored as low-risk or not low-risk, whilst with PESI stratification people can be given intermediate scores.

Benefits and harms

The evidence could not differentiate all-cause mortality, major bleeding, minor bleeding, recurrent pulmonary embolism and total serious adverse events in people with low-risk PE who were treated as outpatients compared to inpatients. The committee noted that because of the nature of studying people with low-risk PE, there are low event numbers for key outcomes, resulting in wide confidence intervals and making it difficult to detect any differences in event numbers between inpatient and outpatient treatment. In contrast, there was no meaningful difference in satisfaction questionnaire scores between inpatient and outpatient groups.

The committee noted that benefits of outpatient treatment included people with PE being in a home environment as opposed to a hospital setting, which is associated with a reduction in risk of infections and in cost of treatment (see cost effectiveness and resource use section below). In addition, people with low-risk PE treated on an outpatient basis had equivalent satisfaction questionnaire scores compared to inpatients.

The committee discussed the risks of treating people with low-risk PE as outpatients, such as being further from acute medical care and medical expertise. They noted that many centres are already treating people with low-risk PE as outpatients in ambulatory units, and that where these centres have robust monitoring pathways, the person with low-risk PE should not experience worse care as an outpatient compared to an inpatient. The committee also highlighted that, in their clinical experience, being in inpatient or outpatient care does not have a large effect on outcome in cases of cardiac arrest induced by clot. They agreed that it was rare to successfully resuscitate PE with cardiac arrest, regardless of setting, due to the nature of a clot-triggered arrest. This suggests mortality rates caused by cardiac arrest would be unlikely to differ between settings.

The committee agreed that, given the findings of this review, the potential benefits and harms, and the fact that outpatient care is already common practice in many places, it may be more useful to view the evidence from a position of non-inferiority (is outpatient treatment less effective or less safe than inpatient treatment?). The

committee noted that the studies could not differentiate between most outcomes of relevance to this review and that this may have been a result of the trial being too small and not being powered as non-inferiority trials. The committee were concerned with this uncertainty as larger trials may have been able to detect a difference (or establish that there is no meaningful difference) between inpatient and outpatient care. However, the committee agreed that in the absence of such trials, the current best evidence did not demonstrate outpatient treatment to be less safe or less effective than inpatient treatment.

Based on these deliberations, the committee made a recommendation in favour of considering outpatient treatment for people with low-risk PE.The committee stressed the importance of using a validated severity score (such as Hestia criteria or PESI) to identify people with low-risk PE who can be provided with outpatient treatment as they were aware that this was not currently the case in all hospitals. However, the committee agreed not to recommend a specific tool or tools because they did not review evidence for the prognostic classification accuracy of the tools used by the studies included in this review and they thought that other suitable tools may exist. The committee noted that stratification of patients into low-risk groups using a validated tool would screen out people with cardiac risks from undergoing outpatient treatment, reducing the chance of adverse events and mortality. Additionally, the committee agreed that although risk stratification could be used to identify people with low-risk PE, the decision to discharge remains a clinical decision and should take into account individual circumstances.

In the absence of any specific evidence relating to the effects of outpatient treatment for people with suspected low-risk PE, the committee agreed that, while awaiting their test results, these people could also be treated on an outpatient basis in the same way as those people with confirmed PE. In addition, the committee included cross references to the diagnosis and interim treatment of PE section of the guideline and to recommendations covering anticoagulation treatment for confirmed DVT or PE to ensure that outpatients with suspected or confirmed low-risk PE respectively were given treatment and baseline blood tests in the same way as inpatients.

The committee noted that regular communication with a medical professional through follow-up and monitoring was imperative to ensuring the safety of outpatients as they undergo treatment. They agreed that the monitoring should match the needs of the individual and that it was possible to manage bleeding risks as an outpatient using these mechanisms. The committee also agreed that it is important that the healthcare practitioner discusses monitoring and the symptoms and signs that should lead the person with low-risk PE to seek help to ensure that the individual can recognise potential health warning signs and allow them to respond appropriately and in a timely manner.

The committee also recognised the importance of providing written information for the person with VTE to refer to as needed, detailing the potential complications of disease, the potential complications of the treatment provided and a clear specialist point of contact for any further queries or concerns. People with VTE should be counselled to contact this service during appropriate times, rather than attend their local emergency department or GP surgery. The committee made a recommendation to reflect these points and to ensure the person with VTE knows what to do if help is needed outside of the specialist service opening hours.

Cost effectiveness and resource use

The committee reflected on the 2017/2018 NHS Reference costs (DZ09N – DZ09Q) for inpatient stays for pulmonary embolism (ranging from approximately £1,500 –

£2,200) and agreed that inpatient treatment is generally more costly than outpatient treatment. The committee noted that outpatient costs could increase if there were higher rates of readmission and complications, but none of the studies included in the evidence review provided any information on these outcomes that would help quantify the impact on costs. The committee also noted that people with low-risk PE in the Aujesky 2011 study received enoxaparin but that the availability of oral anticoagulants could reduce the cost of nurse administration in the outpatient setting. The committee also reflected on other factors that were not captured in the evidence that could impact costs in the inpatient setting; it noted the risk of hospital-acquired infections and the importance of considering the opportunity cost associated with inpatient treatment given the chronic shortage of hospital beds faced by the health service.

Overall, the committee agreed that even with the current gaps in the evidence, outpatient treatment of people with low-risk pulmonary embolism is likely to result in similar outcomes to inpatient treatment but incur lower costs. The committee noted that outpatient treatment is already common practice in many areas and that there may be the potential for cost savings in areas where it is not.

Other factors the committee took into account

The committee discussed whether people with moderate risk PE could also be treated on an outpatient basis. They agreed that they could not make a recommendation on this issue as the current review question was specifically focused on low-risk PE and did not look for evidence relating to outpatient treatment of people with moderate-risk PE. People with moderate risk PE could potentially be identified using the PESI and sPESI tools.

The committee also noted that the different risk stratification scores that are currently in use for selection of outpatient treatment of low-risk PE could have different levels of effectiveness in selecting people with low-risk PE who could be treated as outpatients without needing to be admitted to hospital subsequently. This could have implications for the cost-effectiveness of outpatient treatment too. The current review did not look for evidence on this topic. However, these issues may be used to inform review questions for future updates of this guideline.

1 Appendices

1 Appendix A – Review protocol

2 Review protocol for outpatient treatment.

Field (based on PRISMA-P	Content
Review question	5.1 What is the clinical and cost effectiveness of outpatient treatment for low-risk suspected or confirmed PE?
Type of review question	Intervention
Objective of the review	The surveillance review identified that a lot of treatment of low-risk suspected or confirmed PE is now being undertaken in ambulatory units. This is a change to what was current practice when CG144 was published. Therefore, guidance is now required on whether outpatient treatment is cost effective, and which people with PE should be treated in outpatient units.
Eligibility criteria – population/ disease	Adults (18+ years) with low-risk suspected or confirmed PE. Participants will be considered low-risk if they were classified as low-risk by any validated or non-validated measurement tool that aimed to classify mortality risk rate related to PE (for example GPS, PESI, HESTIA). Analysis will be stratified by low-risk definition if possible. Sensitivity analysis will be performed where studies with non-validated tools are excluded
Eligibility criteria – intervention(s)	Treatment for PE in outpatient settings 'Outpatients' will be defined as people who were discharged within 36 hours after the low-risk acute PE diagnosis who then completed treatment at home. Note: Definition used for 'outpatients' will be reported for each study, and stratification for different definitions will be considered if appropriate.
Eligibility criteria –	Treatment for PE in inpatient settings. 'Inpatient settings' are defined as settings where patients are admitted and provided with a bed for 1 or more nights.

comparator(s)/control	
Outcomes and prioritisation	• All-cause mortality • VTE-related mortality • Recurrence of VTE – Split by recurrent DVT and recurrent PE if data is available • Unplanned admission • Quality of life – Generic and disease-specific measures will be reported – Overall score will be reported (data on subscales will not be reported) • Adverse events – Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
Eligibility criteria – study design	• Randomised controlled trials • Prospective observational studies where there are pre-determined inclusion criteria based on a validated risk tool for PE severity (e.g. HESTIA).
Other inclusion/ exclusion criteria	English language papers only.
Proposed sensitivity/sub-group analysis	• Stratification by score on a validated PE risk tool (e.g. PESI, HESTIA) • People with cancer. • Older people (defined as people over the age of 65) • People who have restricted movement (as defined by the study). • People with learning disabilities. • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease • Stratification by outpatient definition (e.g. discharge within 12 hours vs discharge within 36 hours)

Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C
Identify if an update	This is a new review question for the update of this guideline, therefore no date limit for searches.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	New review question.
Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) of the evidence review.
Methods for assessing bias at outcome/study level	See Appendix B

Criteria for quantitative synthesis (where suitable)	See Appendix B
Methods for analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Assessment of confidence in cumulative evidence	See Appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

PROSPERO registration number	Not applicable.

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Appendix B- Methods

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 3. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 3: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. No MIDs were identified through this process. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. The committee agreed that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. The committee chose not to specify any other MIDs by consensus.

For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

The 'Evidence to Recommendations' section of each review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 4.

Table 4: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Publication bias

Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Appendix C – Literature search strategies

The clinical literature search for RCTs was undertaken by Cochrane, and is outlined in full in the 2019 review. The approach comprises a search to populate the Vascular Trial Register and additional searches of Central, clinical.trialsgov, the IRCTP search portal, Medline, Embase, CINAHL and AMED. The MEDLINE search for this review is presented below.

1 THROMBOSIS/
2 THROMBOEMBOLISM/
3 Venous Thromboembolism/
4 exp Venous Thrombosis/
5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab.
6 exp Pulmonary Embolism/
7 (PE or DVT or VTE).ti,ab.
8 ((vein* or ven*) adj thromb*).ti,ab.
9 (blood adj3 clot*).ti,ab.
10 or/1-9
11 exp OUTPATIENTS/
12 exp Patient Care/
13 exp Ambulatory Care/
14 exp Home Nursing/
15 exp Outpatient Clinics, Hospital/
16 in-patient.ti,ab.
17 inpatient.ti,ab.
18 bed-ridden.ti,ab.
19 exp INPATIENTS/
20 Home Nursing/
21 Outpatient Clinics, Hospital/
22 in-patient.ti,ab.
23 Inpatient*.ti,ab.
24 bed-ridden.ti,ab.
25 out-patient.ti,ab.
26 outpatient.ti,ab.
27 ambulatory*.ti,ab.
28 domicil*.ti,ab.
29 or/11-28
30 randomized controlled trial.pt.
31 controlled clinical trial.pt.
32 randomized.ab.
33 placebo.ab.
34 drug therapy.fs.
35 randomly.ab.
36 trial.ab.
37 groups.ab.
38 or/30-37
39 (2017* or 2018*).ed.
40 10 and 29 and 38 and 39

This search was re run on 4th April 2019 using the NICE inhouse RCT filter.

An additional search was undertaken on 26th November 2018 to identify observational (non-RCT) studies in Medline, Medline in Process, Medline Epub Ahead of Print, Embase,(Ovid platform) Cochrane Database of Systematic Reviews (Wiley platform) and DARE (Centre for

Reviews and Dissemination platform). This search was re run on 4th April 2019.The Medline strategy is presented below. The NICE inhouse observational studies filter was used.

1 exp Pulmonary Embolism/
2 ((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).tw.
3 (pulmonary adj infarction).tw.
4 or/1-3
5 exp OUTPATIENTS/
6 exp INPATIENTS/
7 exp Ambulatory Care/
8 home care services/ or home care services, hospital-based/ or home health nursing/
9 exp HOSPITALIZATION/
10 exp Ambulatory Care Facilities/
11 ((in-patient* or inpatient*) adj4 (care* or treat* or service* or pathway* or protocol* or therap* or nurs* or support* or unit* or setting*)).tw.
12 hospitali*.tw.
13 (home* adj4 (care* or treat* or service* or pathway* or protocol* or therap* or nurs* or support* or unit* or setting*)).tw.
14 ((out-patient* or outpatient*) adj4 (care* or treat* or service* or clinic* or pathway* or protocol* or therap* or nurs* or support* or unit* or setting*)).tw
15 ambulatory.tw.
16 (domicil* adj4 (care* or treat* or service* or pathway* or protocol* or therap* or nurs* or support* or unit* or setting*)).tw.
17 (PESI or sPESI or "pulmonary embolism severity index" or HESTIA or "ESC criteria" or "european society of cardiology criteria" or GPS).tw.
18 (Risk adj1 (tool* or score* or stratify or stratification)).tw.
19 (Predict* adj1 (rule* or tool* or score*)).tw.
20 or/5-19
21 4 and 20
22 Observational Studies as Topic/
23 Observational Study/
24 Epidemiologic Studies/
25 exp Case-Control Studies/
26 exp Cohort Studies/
27 Cross-Sectional Studies/
28 Controlled Before-After Studies/
29 Historically Controlled Study/
30 Interrupted Time Series Analysis/
31 Comparative Study.pt.
32 case control$.tw.
33 case series.tw.
34 (cohort adj (study or studies)).tw.
35 cohort analy$.tw.
36 (follow up adj (study or studies)).tw.
37 (observational adj (study or studies)).tw.
38 longitudinal.tw.
39 prospective.tw.
40 retrospective.tw.
41 cross sectional.tw.
42 or/22-41
43 21 and 42
44 animal/ not human/
45 43 not 44
46 limit 45 to english language

Searches to identify economic evidence were run on 29th November 2018.in Medline , Medline In Process Embase and Econlit (Ovid platform) and NHS EED and the Health Technology Database (Centre for Reviews and Dissemination platform). NICE inhouse economic evaluation and quality of life filters were attached to lines 1 to 21 of the above strategy for searches in the Medline and Embase databases. A single search to identify economic evidence across all questions was re run on 9th April 2019. Medline versions of the filters are displayed below.

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of Life

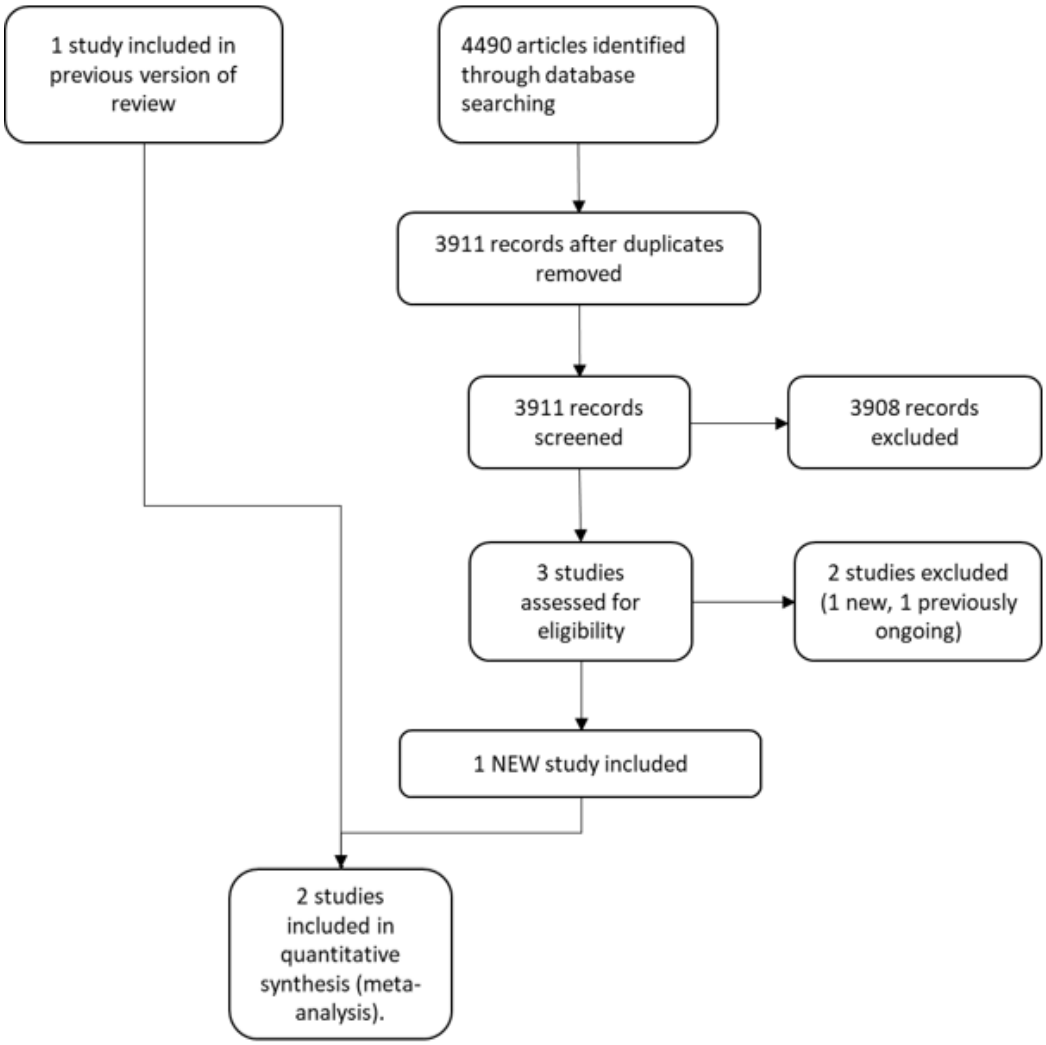
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/ (22343)
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

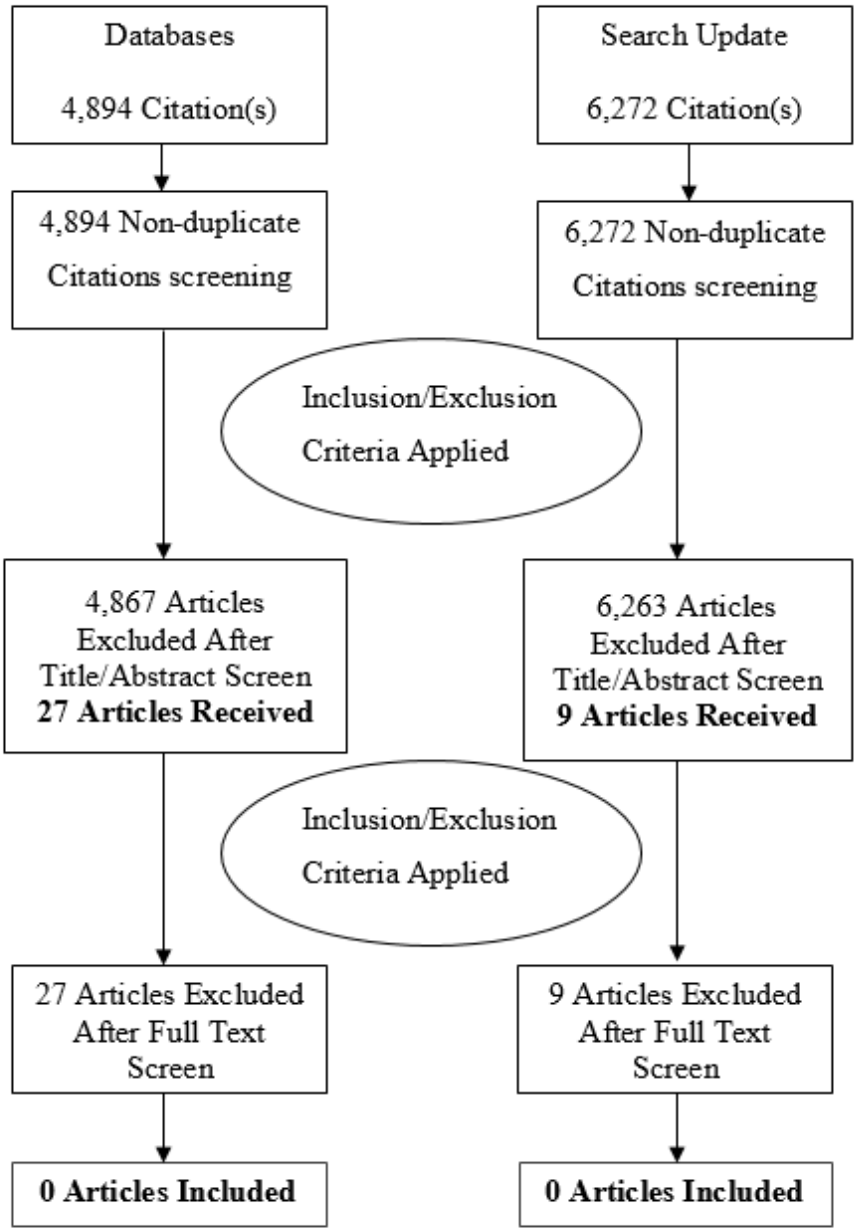
Appendix D – Clinical evidence study selection

Randomized controlled trials

The following diagram is based on the study flow diagram from the Yoo et al. 2019 Cochrane review.



Prospective observational studies



Appendix E – Clinical evidence tables

Systematic review

Yoo et al. 2019

Study type	Systematic review
Databases searched	• Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched on 28 March 2018); • Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO 2018, Issue 2); • MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (searched from 1 January 2017 to 26 March 2018); • Embase Ovid (searched from 1 January 2017 to 26 March 2018); • CINAHL Ebsco (searched from 1 January 2017 to 26 March 2018); • AMED Ovid (searched from 1 January 2017 to 28 March 2018).
Study inclusion criteria	• Outpatient vs inpatient comparison • RCTs and Quasi-RCTs ((RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods)
Study exclusion criteria	• Study did not meet the specified inclusion criteria
Participant inclusion criteria	• Adults (18 years and older) diagnosed with low-risk acute pulmonary embolism (PE) • Participant allocated to home (outpatient) management for acute PE (discharged within 36 hours) • Participant allocated to hospital (inpatient) management for acute PE
Participant exclusion criteria	• Participants did not meet the specified inclusion criteria
Interventions	• Outpatient treatment of adults with low-risk PE • Inpatient treatment of adults with low-risk PE
Outcome measures	• Short-term all-cause mortality (from the date of randomisation to 7-10 days) • Long-term all-cause mortality (from the date of randomisation to 90 days) • Bleeding (from the date of randomisation to 90 days): • Adverse effects such as haemodynamic instability (from the date of randomisation to 90 days) • Recurrence of PE (from the date of randomisation to 90 days) • Participant satisfaction or compliance, or both (from the date of randomisation to 90 days)
Risk of bias	• Study eligibility and criteria: Low risk of bias *Review adhered to pre-defined objectives and eligibility criteria. Eligibility criteria were appropriate for review question, unambiguous and without inappropriate restrictions*.

Study type	Systematic review
	• Identification and selection of studies: Low risk of bias *Databases searched: Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase Ovid, CINAHL, and AMED Ovid (searched from 1 January 2017 to 26th/28th March 2018*). • Data collection and study appraisal: Low risk of bias *Sufficient study characteristics were provided, all relevant study results were collected and a formal risk of bias assessment was conducted.* • Synthesis and findings: Low risk of bias *All relevant identified studies were included in the evidence synthesis and all pre-defined analyses were reported. Minimal bias detected*. • Overall risk of bias: Low • Applicability: Partially applicable *The identified review fully covers a discrete subsection of the review protocol in the guideline- only covers RCTs.*

Randomised controlled trials

The following evidence tables and judgements of risk of bias were taken from the Yoo et al. 2019 Cochrane review. The overall study level risk of bias and directness was determined by the Guideline Updates Team based on the Cochrane review tables (Table 5).

Aujesky 2011

Study type	Details
Methods	Design: international, open-label, randomised, non-inferiority trial Multicentre study: 19 EDs in Switzerland, France, Belgium and the US Period: February 2007 to June 2010 Sample size: justified (160 participants per treatment group would provide 80% power to detect a non-inferiority margin of 4% using a 1-sided α of 0.05, assuming a 5% drop-out rate) Follow-up: 90 days after randomisation
Participants	344 eligible participants randomised, but only 339 included in primary analysis; 337 completed follow-up and 317 were included in per-protocol analysis. In the outpatient group (171 participants): 84 men, 87 women, mean age 47 years; inpatient group (168 participants): 85 men, 83 women, mean age 49 years. Inclusion criteria: aged ≥ 18 years with acute, symptomatic and objectively verified PE who were at low risk of death based on PESI (risk classes I or II) Exclusion criteria: arterial hypoxaemia, SBP < 100 mmHg, chest pain necessitating parenteral opioids, active bleeding, high risk of bleeding, gastrointestinal bleeding, severe renal failure, extreme obesity, history of HIT or allergy to heparins, therapeutic oral anticoagulation at the time of diagnosis of PE, pregnancy, diagnosis of PE > 23 hours before the time of screening.

Study type	Details
Interventions	Outpatient (172 participants): subcutaneous enoxaparin 1 mg/kg twice daily and discharged from the ED within 24 hours of randomisation. If self-injection was not possible, a study nurse either taught a caregiver to give the enoxaparin or arranged administration by a visiting nurse. Inpatient (172 participants): subcutaneous enoxaparin 1 mg/kg twice daily and admitted to hospital. All participants also received vitamin K antagonist therapy
Outcomes	Primary outcome: recurrence of symptomatic confirmed VTE defined as recurrent PE or new or recurrent DVT within 90 days of randomisation. Secondary outcomes: overall satisfaction, major bleeding within 14 and 90 days of randomisation, all-cause mortality within 90 days.
Notes	Diagnostic criteria for recurrent PE were a new intraluminal filling defect on spiral CT or pulmonary angiography or a new perfusion defect of a lung segment with corresponding normal ventilation by lung scan or confirmation of a new PE on autopsy. Diagnostic criteria for DVT were the non-compressibility of a new venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography, or a new intraluminal filling defect on contrast venography. Overall satisfaction was assessed by a non-validated 5-point Likert scale questionnaire. Participants completed this questionnaire by telephone 14 days after randomisation. Major bleeding was defined as fatal bleeding, bleeding at critical sites (i.e. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome), or bleeding with a reduction of haemoglobin of ≥ 20 g/L or resulting in transfusion of ≥ 2 units of packed red cells. Authors of the study declared they received grants, honoraria, consultancy fees, and payments from the pharmaceutical industry which sponsored the study. However, both regimens (outpatient or inpatient) patients received the same treatment.
Risk of bias	Random sequence generation: Low risk *The eligible patients were allocated to outpatient treatment or inpatient treatment groups in a one to one ratio with a randomised block design generated from a password protected computer web page* Allocation concealment: Low risk *The patients were stratified by site and using small fixed block sizes (2 or 4). Quote: "To balance recruitment in time and preclude enrolment bias, the blocks varied randomly from two to four patients"* Blinding of outcome assessment: Low risk *Although the paper says that the analysers were unmasked to treatment group assignment, there was a committee unaware of treatment assignment which confirmed all outcomes.* *Quote: "A committee of three clinical experts from the University Hospital of Lausanne (Switzerland) who were unaware of treatment assignment confirmed all outcomes and classified the cause of all deaths as definitely due to pulmonary embolism, possibly due to pulmonary embolism (e.g., sudden death without obvious cause), due to major bleeding, or due to another cause."* Incomplete outcome data: Low risk *Although the paper says that the analysers were unmasked to treatment group assignment, there was a committee unaware of treatment assignment which confirmed all outcomes.* *Quote: "A committee of three clinical experts from the University Hospital of Lausanne (Switzerland) who were unaware of treatment assignment*

Study type	Details
	confirmed all outcomes and classified the cause of all deaths as definitely due to pulmonary embolism, possibly due to pulmonary embolism (e.g., sudden death without obvious cause), due to major bleeding, or due to another cause." Selective reporting: Low risk *No evidence of selecting reporting* Other bias: Low risk *We did not find aspects of methodology that might be been influenced by vested interests and which may lead directly to a risk of bias.* **Overall risk of bias – Low** **Applicability- Directly applicable**

Peacock 2018

Study type	Details
Methods	Design: international, open-label, randomised, parallel group, multicentre Multicentre study: 35 sites in United States Sample size: 114 Follow-up: 90 days after randomisation
Participants	Inclusion criteria: adult patients (age ≥ 18 years) with objectively confirmed PE (with or without symptomatic DVT) who are deemed to be at low risk for recurrent VTE, major bleeding, or all-cause mortality based on Hestia criteria, and a life expectancy of at least 6 months. The authors adapted the Hestia criteria by removing the 24-hour time markers. Exclusion criteria: women of child-bearing age with no use of a highly effective birth control method, patients with any Hestia criteria present, any concomitant contraindicated medications, and individuals with contraindications to anticoagulant therapy, allergies to rivaroxaban, or having barriers to treatment adherence or follow-up
Interventions	Intervention (51): outpatient treatment with rivaroxaban 15 mg orally twice daily for the first 21 days followed by 20 mg orally once daily for approximately 69 days for a total treatment duration of 90 days Comparison (63): local standard-of-care, participants received local standard-of-care as per local protocol and defined by the medical team caring for the participant, which typically involves bridging therapy and hospitalisation, but may also include any of the NOACs.
Outcomes	Mean duration of hospitalisation expressed in hours for venous thromboembolic or bleeding events, in the 30 days after randomisation Major bleeding based on the International Society on Thrombosis and Haemostasis (ISTH) within 90 days Percentage of participants with new/recurrence of VTE, or VTE-related death, within 7, 14, 30, or 90 days from randomisation

Study type	Details
	Percentage of participants with number of unplanned hospital visits or physician office for VTE symptoms and/or bleeding (up to 7, 14, 30 and 90 days) Mean combined duration of initial and subsequent ED hospitalisation for any reason (up to 30 and 90 days) Percentage of participants satisfied using site-of-care satisfaction questionnaire (day 7) and by ACTS (day 90) Clinically relevant non major bleeding, based on ISTH definitions Total, all-cause mortality Total, serious adverse events Costs
Notes	Sponsored by a pharmaceutical industry (Janssen Pharmaceuticals, Raritan, NJ) The authors used the Hestia criteria to classify patients, therefore we considered that most patients were symptomatic.
Risk of bias	Random sequence generation: Low risk *They used an interactive Web system.* *Quote: After obtaining written informed consent, patients were randomly assigned in a 1:1 ratio to ED discharge on open-label rivaroxaban or standard care (as determined by the attending physician) by an interactive Web system within 12 hours of diagnosis.* Allocation concealment: Low risk *They used an interactive web system.* *Quote: After obtaining written informed consent, patients were randomly assigned in a 1:1 ratio to ED discharge on open-label rivaroxaban or standard care (as determined by the attending physician) by an interactive Web system within 12 hours of diagnosis.* Blinding of the outcome assessment: Low risk *The analysers were masked to treatment group assignment* *Quote: "Principal investigators and outcome adjudicators were masked to group assignment".* Incomplete outcome data: Unclear risk *Less than 20% of drop-outs and withdrawals (7 participants in the outpatient group and 8 participants in the inpatient group), however the authors did not perform intention to treat analysis. All outpatients completed the study and authors could confirm that all of them were alive, however in inpatient group they could not confirm this for two patients.* Selective reporting: Low risk *No evidence of selective reporting.* Other bias: Low risk *We did not find aspects of methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. However, comparison of two sites of care (inpatient vs outpatient) was imbalanced by different pharmacotherapy between the arms:* *The outpatient group received 15 mg oral rivaroxaban twice daily for the first 21 days, followed by 20 mg oral rivaroxaban once daily for*

Study type	Details
	approximately 69 days for a total treatment duration of 90 days. The inpatient comparison group received local standard-of-care, as per local protocol and defined by the medical team caring for the participant, which typically involved intravenous UFH or subcutaneous low LMWH and hospitalisation, but also included any of the NOACs (75% of all patients were initially treated with unfractionated or low-molecular-weight heparin but ultimately received NOACs, most commonly rivaroxaban (51%) or apixaban (25%)). **Overall risk of bias – Low** **Applicability- Directly applicable**

Table 5: Overall study risk of bias and directness with reasons for judgement

Author	Risk of Bias	Reason	Directness
Aujesky 2011	Low	All risks low bar attrition bias, which was unclear	Directly applicable
Peacock 2018	Low	All risks low bar attrition bias, which was unclear	Directly applicable

Appendix F – Forest plots

The results in the forest plots in Figures 1 to 7 are taken from the Yoo et al. 2019 Cochrane review, but the choice of model (FE or RE models) used was based on methods described in appendix B. Figure 8 was compiled by the Guideline Updates Team.

Figure 1: Short-term all-cause mortality

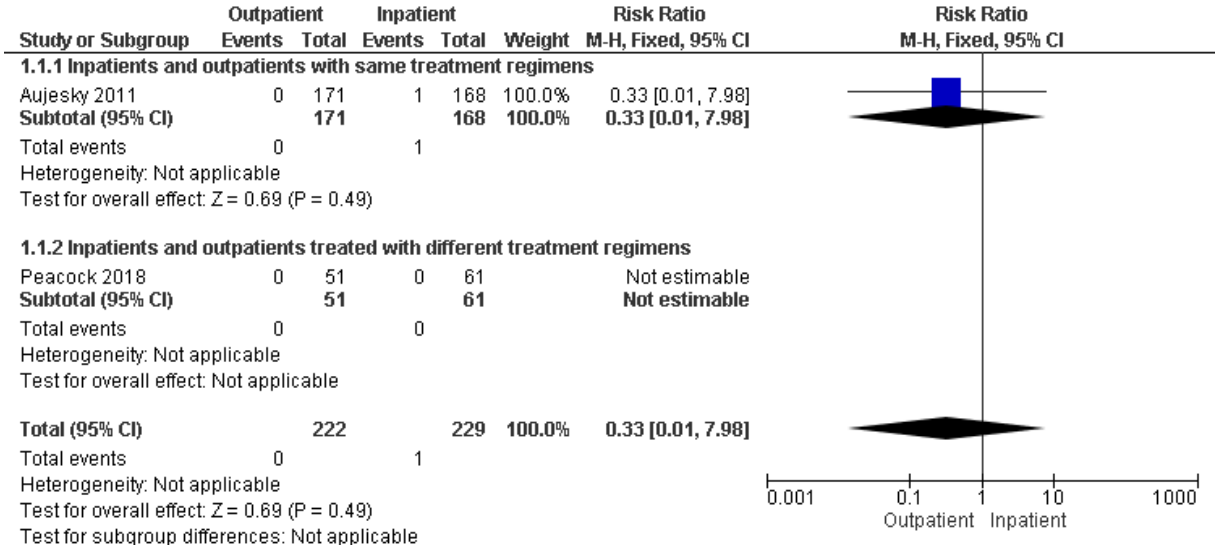


Figure 2: Long-term all-cause mortality

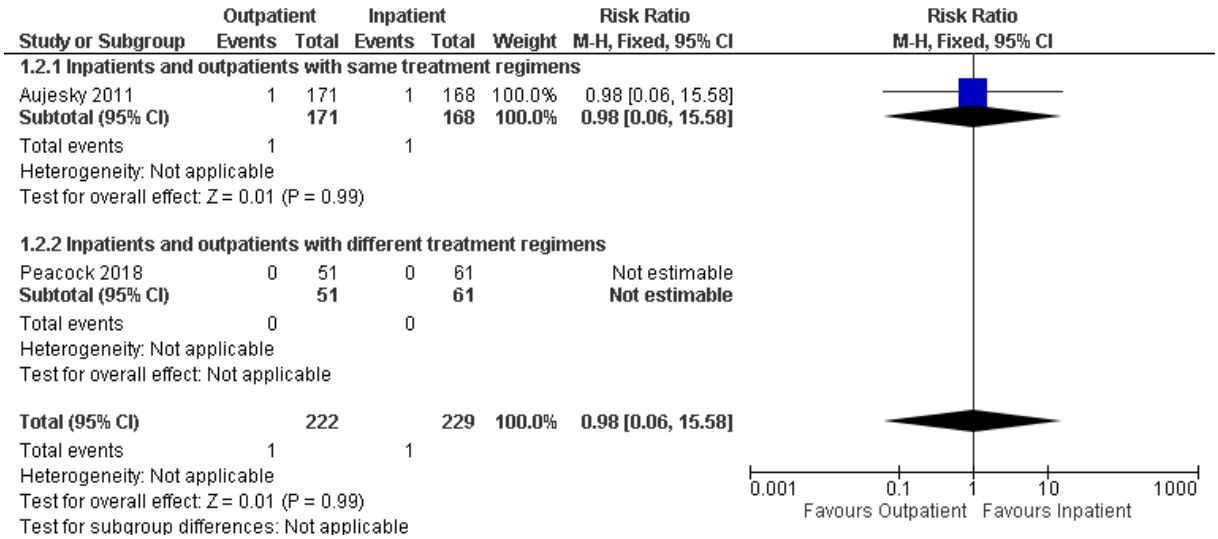


Figure 3: Major bleeding within 14 days

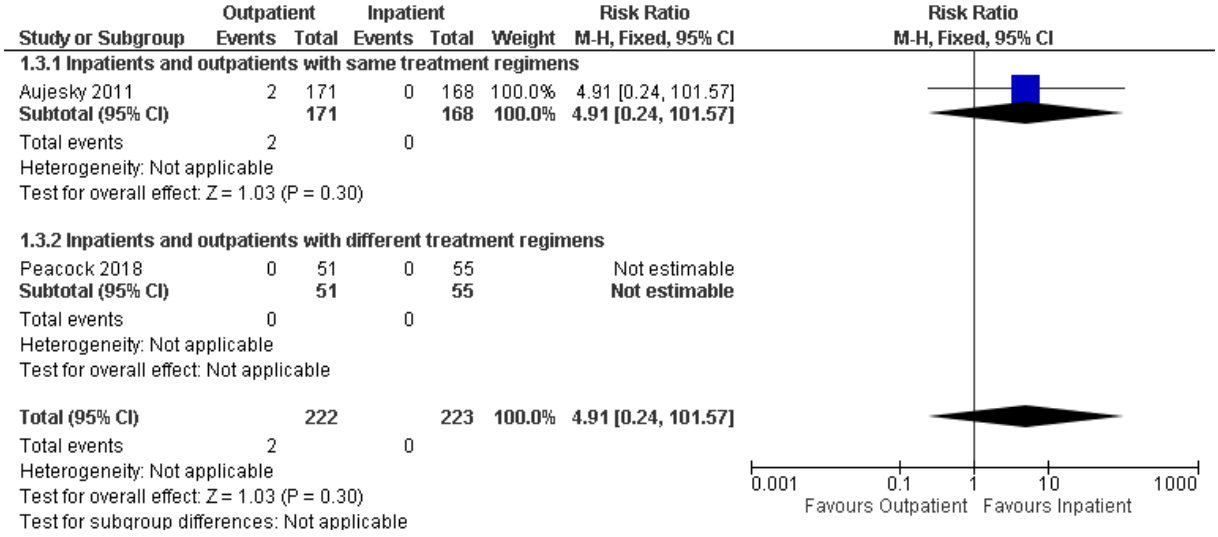


Figure 4: Major bleeding within 90 days

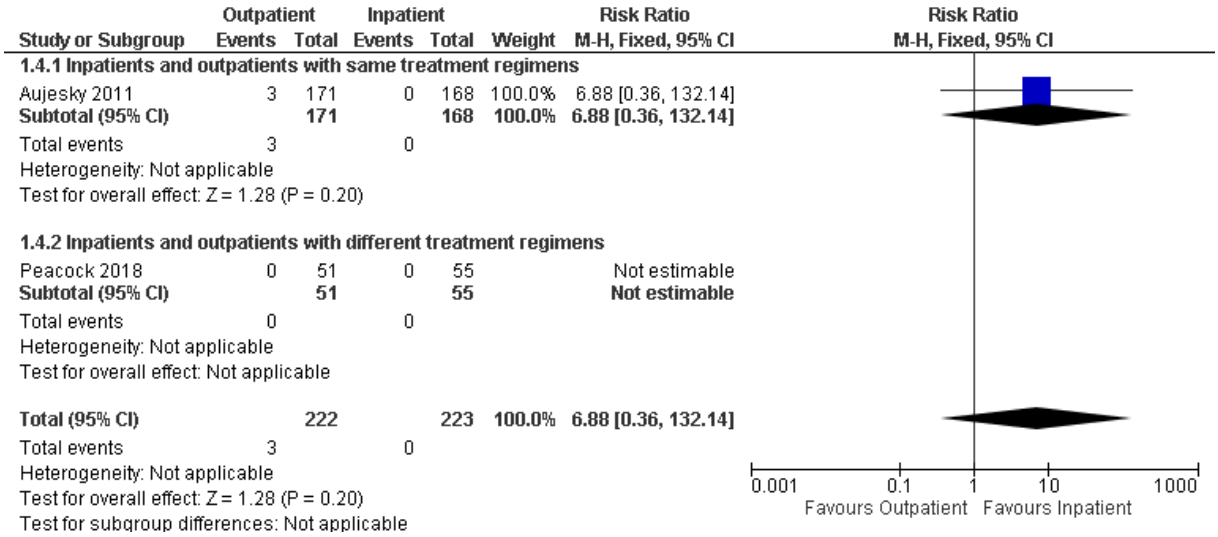


Figure 5: Minor bleeding

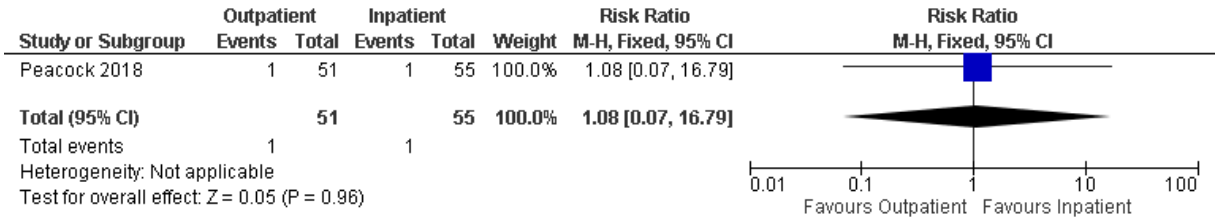


Figure 6: Recurrent pulmonary embolism within 90 days

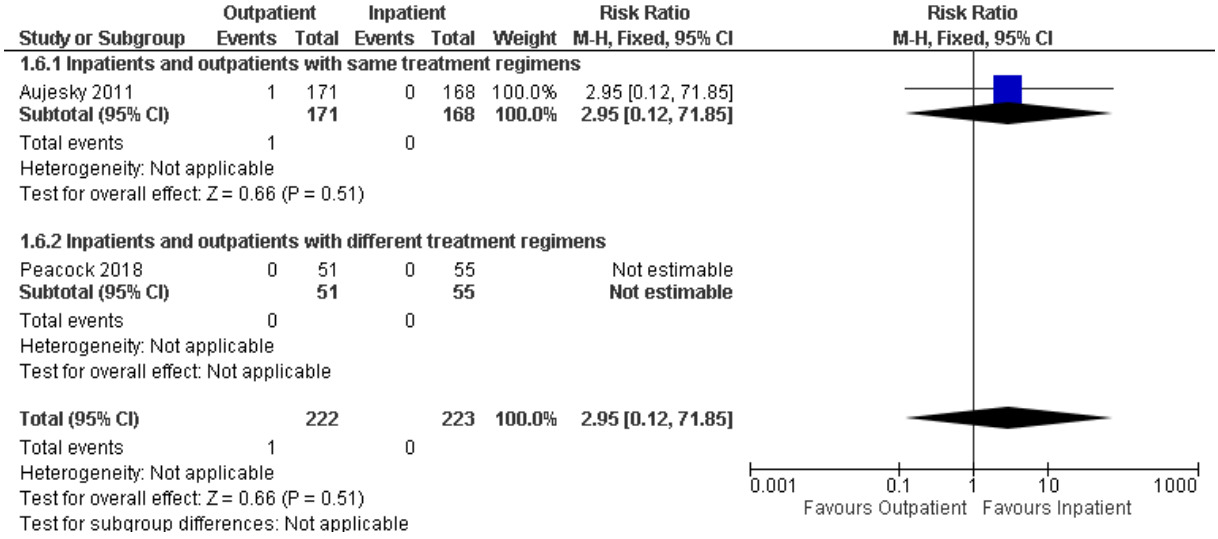


Figure 7: Satisfaction questionnaire

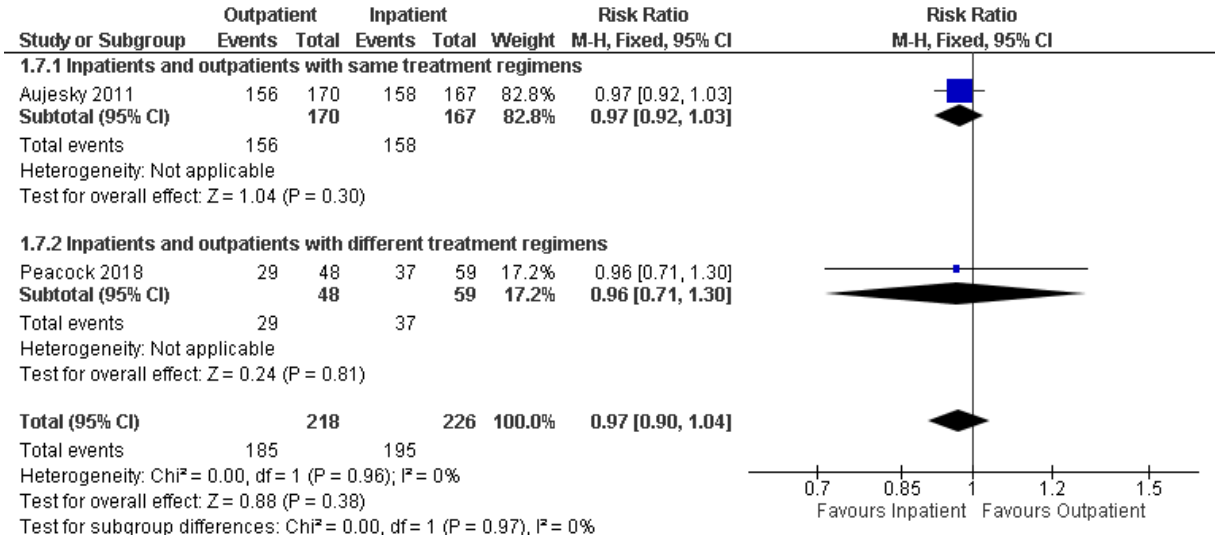
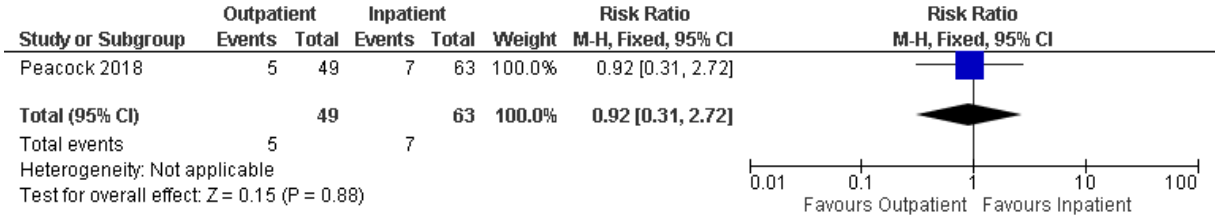


Figure 8: Total serious adverse events (FDA/EMA definition)



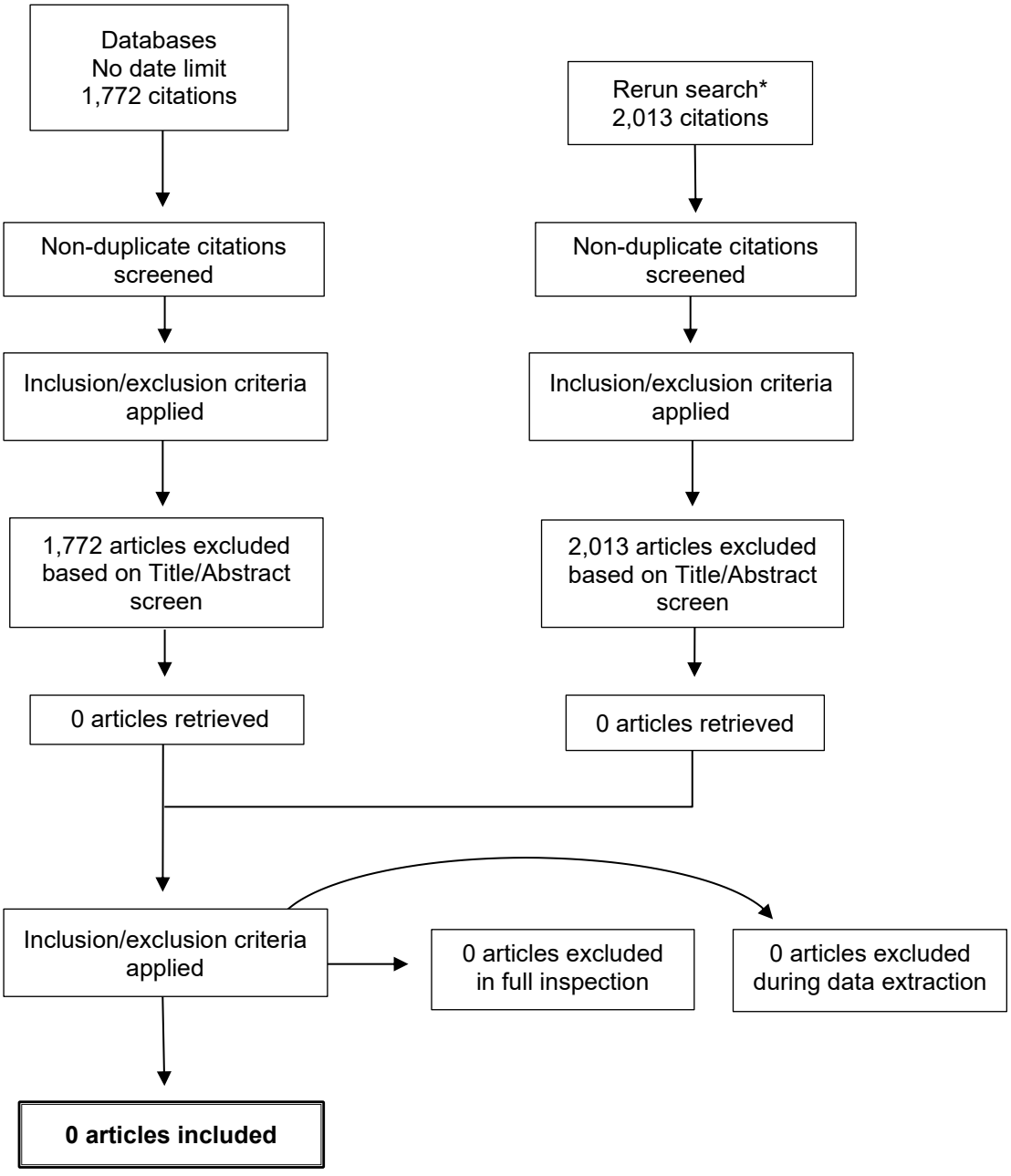
Appendix G – GRADE tables

Quality assessment						No of patients		Effect			
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Outpatient	Inpatient	Relative (95% CI)	Absolute risk: Control (Inpatient)	Absolute risk: Intervention (Outpatient) (95% CI)	Quality
Short-term all-cause mortality (>1 favours inpatient)											
2	RCT	Not serious	Not serious	N/A[2]	Serious[3]	0/222	1/229	RR 0.33 (0.01, 7.98)	0.44 per 100	0.14 per 100 (0.01, 3.49)	Moderate[5]
Long-term all-cause mortality (>1 favours inpatient)											
2	RCT	Not serious	Not serious	N/A[2]	Serious[3]	1/222	1/229	RR 0.98 (0.06, 15.58)	0.44 per 100	0.43 per 100 (0.03, 6.80)	Moderate[5]
Major bleeding within 14 days (>1 favours inpatient)											
2	RCT	Not serious	Not serious	N/A[2]	Very serious[4]	2/222	0/223	RR 4.91 (0.24, 101.57)	Not calculable[1]	Not calculable[1]	Low
Major bleeding within 90 days (>1 favours inpatient)											
2	RCT	Not serious	Not serious	N/A[2]	Very serious[4]	3/222	0/223	RR 6.88 (0.36, 132.14)	Not calculable[1]	Not calculable[1]	Low
Minor bleeding (>1 favours inpatient)											
1 (Peacock 2018)	RCT	Not serious	Not serious	N/A	Very serious[4]	1/51	1/55	RR 1.08 (0.07, 16.79)	1.82 per 100	1.96 per 100 (0.13, 32.93)	Low
Recurrent PE within 90 days (>1 favours inpatient)											
2	RCT	Not serious	Not serious	N/A[2]	Very serious[4]	1/222	0/223	RR 2.95 (0.12, 71.85)	Not calculable[3]	Not calculable[1]	Low

Quality assessment						No of patients		Effect			
No. of studies	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Outpatient	Inpatient	Relative (95% CI)	Absolute risk: Control (Inpatient)	Absolute risk: Intervention (Outpatient) (95% CI)	Quality
Satisfaction questionnaire (>1 favours outpatient)											
2	RCT	Not serious	Not serious	Not serious	Not serious	185/218	195/225	RR 0.97 (0.9, 1.04)	86.28 per 100	83.59 per 100 (77.89, 89.70)	High
Total serious adverse events - FDA/EMA definition (>1 favours inpatient)											
1 (Peacock 2018)	RCT	Not serious	Not serious	N/A	Very serious[4]	5/49	7/63	RR 0.92 (0.31, 2.72)	11.11 per 100	10.2 per 100 (3.45, 30.20)	Low

1. Absolute risk could not be calculated due to 0 events recorded in the inpatient arm.
2. Inconsistency was non-applicable as one study reported 0 events and therefore did not contribute to the meta-analysis
3. 95% confidence interval crosses the line of no effect.
4. 95% confidence interval crosses both ends of the defined MID interval (0.8, 1.25)
5. The quality rating reported here differs from the one reported in the Cochrane review (Yoo, 2019). They rated the evidence as low quality (downgraded by two levels) because of overall small sample size, small number of events, imprecision in the confidence intervals and the fact that publication bias could not be discounted. The Guideline Updates Teams followed methodology outlined in appendix B and this led to the difference in quality rating.

Appendix H – Economic evidence study selection



**Combined for all questions in the guideline*

Appendix I – Excluded studies

Clinical studies

Randomised controlled trials excluded by Yoo et al. 2019

Study	Reason for exclusion
den Exter PL, Zondag W, Klok FA, Brouwer RE, Dolsma J, Eijsvogel M, et al. Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without N-terminal pro–brain natriuretic peptide testing in patients with acute pulmonary embolism. American Journal of Respiratory and Critical Care Medicine 2016;194(8):998-1006.	Patients were randomised to either outpatient treatment or to management based on NT-pro BNP levels, and not to either home or inpatient management
Roy PM, Gable B. Hospitalization or Out-treatment ManagEment of Patients with Pulmonary Embolism: a randomized controlled trial (HOME-PE). clinicaltrials.gov/ct2/show/NCT02811237 (first posted 23 June 2016).	Patients were randomised to either Hestia or PESI management, and non-randomised to either inpatient or outpatient treatment
Kovacs MJ, Rodger M, Anderson DR, Morrow B, Kells G, Kovacs J, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. Annals of Internal Medicine 2003;138(9):714-9. [CRSREF: 3381864]	RCT which evaluated different doses of warfarin in outpatients
Otero R, Uresandi F, Jiménez D, Cabezudo MA, Oribe M, Nauffal D, et al. Home treatment in pulmonary embolism. Thrombosis Research 2010;126(1):e1-5. [CRSREF: 3381866]	RCT which evaluated 3 to 5 days in the hospital as 'outpatients'
Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. Journal of Thrombosis and Haemostasis 2011;9(8):1500-7. [CRSREF: 3381868]	Cohort study

Observational studies excluded by the Guideline Updates Team (main search)

Study	Reason for exclusion
Aujesky, D.; Roy, P. M.; Verschuren, F.; Righini, M.; Osterwalder, J.; Egloff, M.; Renaud, B.; Verhamme, P.; Stone, R. A.; Legall, C.; Sanchez, O.; Pugh, N. A.; N'Gako, A.; Cornuz, J.; Hugli, O.; Beer, H. J.; Perrier, A.; Fine, M. J.; Yealy, D. M., Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial, Lancet, 378, 9785, 41-8, 2011	**Randomised controlled trial already included in RCT part of review**
Belcaro, G.; Nicolaides, A. N.; Cesarone, M. R.; Laurora, G.; De Sanctis, M. T.; Incandela, L.; Barsotti, A.; Corsi, M.; Vasdekis, S.; Christopoulos, D.; Lennox, A.; Malouf, M., Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis, Angiology, 50, 10, 781-7, 1999	**Does not contain a population of people with PE**
Bledsoe, J. R.; Woller, S. C.; Stevens, S. M.; Aston, V.; Patten, R.; Allen, T.; Horne, B. D.; Dong, L.; Lloyd,	**Study does not contain a relevant intervention**

J.; Snow, G.; Madsen, T.; Elliott, C. G., Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study, Chest, 154, 2, 249-256, 2018	[No separate inpatient and outpatient groups]
Chong, B. H.; Brighton, T. A.; Baker, R. I.; Thurlow, P.; Lee, C. H.; Group, Asth Dvt Study, Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis, Journal of Thrombosis & Thrombolysis, 19, 3, 173-81, 2005	**Does not contain a population of people with PE** [PE set as exclusion criteria in study]
Crouser, N.; Malik, A. T.; Jain, N.; Yu, E.; Kim, J.; Khan, S. N., Discharge to Inpatient Care Facility After Vertebroplasty/Kyphoplasty: Incidence, Risk Factors, and Postdischarge Outcomes, World Neurosurgery, 118, e483-e488, 2018	**Not a relevant study design** [Retrospective cohort study]
Dahl, O. E.; Gudmundsen, T. E.; Bjornara, B. T.; Solheim, D. M., Risk of clinical pulmonary embolism after joint surgery in patients receiving low-molecular-weight heparin prophylaxis in hospital: a 10-year prospective register of 3,954 patients, Acta Orthopaedica Scandinavica, 74, 3, 299-304, 2003	**Study does not contain a relevant intervention** [No comparison between outpatients and inpatients]
Duroux, P.; Ninet, J.; Bachet, Ph.; Prandoni, P.; Ruol, A; Vigo, M.; Barret, A.; Mericq, O.; Boneu, B.; Janvier, G.; Girard, Ph.; Laprevote-Heully, M.C.; Sourou, P.; Robert, D.; Chagny, M.; Nenci, G.; Nency Agnelli, G.G.; d'Addato, M.; Palumbo, H.; Bachmann, Fedor., A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study, Thrombosis & Haemostasis, 65, 3, 251-6, 1991	**Does not contain a population of people with PE** [PE set as exclusion criteria in study] **Study does not contain a relevant intervention** [Does not include outpatients]
Fang, M. C.; Fan, D.; Sung, S. H.; Witt, D. M.; Schmelzer, J. R.; Steinhubl, S. R.; Yale, S. H.; Go, A. S., Validity of Using Inpatient and Outpatient Administrative Codes to Identify Acute Venous Thromboembolism: The CVRN VTE Study, Medical Care, 55, 12, e137-e143, 2017	**Not a relevant study design** [Retrospective chart review]
Federman, A. D.; Soones, T.; DeCherrie, L. V.; Leff, B.; Siu, A. L., Association of a bundled hospital-at-home and 30-day postacute transitional care program with clinical outcomes and patient experiences, JAMA Internal Medicine, 178, 8, 1033-1041, 2018	**Does not contain a population of people with PE** [Study includes mixed disease population but doesn't report data on PE subgroup]
Huang, W.; Goldberg, R. J.; Anderson, F. A.; Cohen, A. T.; Spencer, F. A., Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: population-based Worcester Venous Thromboembolism Study, Journal of Thrombosis & Thrombolysis, 41, 3, 525-38, 2016	**Not a relevant study design** [Retrospective cohort study]
Isene, R.; Bernklev, T.; Hoie, O.; Langholz, E.; Tsianos, E.; Stockbrugger, R.; Odes, S.; Smastuen, M.; Moum, B.; Group, Ec-Ibd Study, Thromboembolism in inflammatory bowel disease: results from a prospective, population-based European inception cohort, Scandinavian Journal of Gastroenterology, 49, 7, 820-5, 2014	**Does not contain a population of people with PE** [Not recruited on basis of having PE, PE is an outcome, Inclusion criteria Age >16 years not age >18 years old]
Lozano, F.; Trujillo-Santos, J.; Barron, M.; Gallego, P.; Babalis, D.; Santos, M.; Falga, C.; Monreal, M.; Investigators, Riete, Home versus in-hospital treatment of outpatients with acute deep venous	**Does not contain a population of people with PE** [PE set as exclusion criteria in study]

thrombosis of the lower limbs, Journal of Vascular Surgery, 59, 5, 1362-7.e1, 2014	
Lui, B.; Tran, A.; Montalto, M., Treatment of patients with pulmonary embolism entirely in Hospital in the Home, Australian Family Physician, 36, 5, 381-4, 2007	**Not a relevant study design** [Retrospective study]
Otero, R.; Uresandi, F.; Jimenez, D.; Cabezudo, M. A.; Oribe, M.; Nauffal, D.; Conget, F.; Rodriguez, C.; Cayuela, A., Home treatment in pulmonary embolism, Thrombosis Research, 126, 1, e1-5, 2010	**Study does not contain a relevant intervention** [Outpatient group not discharged until 3rd day (>36 hours)] **Not a relevant study design** [RCT, not included here because this search was aimed at identifying observational studies. Not included in RCT part of review based on intervention (see RCT exclusion table above).]
Ozcan Cetin, E. H.; Cetin, M. S.; Canpolat, U.; Akdi, A.; Aras, D.; Temizhan, A.; Aydogdu, S., Platelet-to-lymphocyte ratio as a novel marker of in-hospital and long-term adverse outcomes among patients with acute pulmonary embolism: A single center large-scale study, Thrombosis Research, 150, 33-40, 2017	**Not a relevant study design** [Risk score calculated retrospectively]
Maestre, A.; Sanchez, R.; Rosa, V.; Aujesky, D.; Lorenzo, A.; Barillari, G.; Monreal, M.; Investigators, Riete, Clinical characteristics and outcome of inpatients versus outpatients with venous thromboembolism: findings from the RIETE Registry, European Journal of Internal Medicine, 21, 5, 377-82, 2010	**Study does not contain a relevant intervention** [No stratification of results between inpatients and outpatients in PE population]
Stewart, M.; Bledsoe, J.; Madsen, T.; Sturges, Z.; McGuire, T.; Rayner, T.; Hamilton, D.; Barton, E., Utilization and Safety of a Pulmonary Embolism Treatment Protocol in an Emergency Department Observation Unit, Critical Pathways in Cardiology: A Journal of Evidence-Based Medicine, 14, 3, 87-9, 2015	**Study does not contain a relevant intervention** [No outpatient cohort]
Zondag, W.; den Exter, P. L.; Crobach, M. J.; Dolsma, A.; Donker, M. L.; Eijsvogel, M.; Faber, L. M.; Hofstee, H. M.; Kaasjager, K. A.; Kruip, M. J.; Labots, G.; Melissant, C. F.; Sikkens, M. S.; Huisman, M. V.; Hestia Study, Investigators, Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism, Thrombosis & Haemostasis, 109, 1, 47-52, 2013	**Not a relevant study design** [Risk score calculated retrospectively]
Zondag, W.; Hiddinga, B. I.; Crobach, M. J.; Labots, G.; Dolsma, A.; Durian, M.; Faber, L. M.; Hofstee, H. M.; Melissant, C. F.; Ullmann, E. F.; Vingerhoets, L. M.; de Vreede, M. J.; Huisman, M. V.; Hestia Study, Investigators, Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism, European Respiratory Journal, 41, 3, 588-92, 2013	**Study does not contain a relevant intervention** [Retrospective review of people excluded from home treatment]
Zondag, W.; Vingerhoets, L. M.; Durian, M. F.; Dolsma, A.; Faber, L. M.; Hiddinga, B. I.; Hofstee, H. M.; Hoogerbrugge, A. D.; Hovens, M. M.; Labots, G.; Vlasveld, T.; de Vreede, M. J.; Kroft, L. J.; Huisman, M. V.; Hestia Study, Investigators, Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function, Journal of Thrombosis & Haemostasis, 11, 4, 686-92, 2013	**Does not contain a population of people with PE** [High-risk population included in study with low-risk population and used to stratify inpatient and outpatient separately.]

Jamal, M. H.; Corcelles, R.; Shimizu, H.; Kroh, M.; Safdie, F. M.; Rosenthal, R.; Brethauer, S. A.; Schauer, P. R., Thromboembolic events in bariatric surgery: a large multi-institutional referral center experience, Surgical Endoscopy, 29, 2, 376-380, 2015	**Does not contain a population of people with PE** [Study did not recruit people with PE]
Kahn, S. R.; Akaberi, A.; Granton, J. T.; Anderson, D. R.; Wells, P. S.; Rodger, M. A.; Solymoss, S.; Kovacs, M. J.; Rudski, L.; Shimony, A.; Dennie, C.; Rush, C.; Hernandez, P.; Aaron, S. D.; Hirsch, A. M., Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study, American Journal of Medicine, 130, 8, 990.e9-990.e21, 2017	**Study does not contain a relevant intervention** [No stratification of results between inpatients and outpatients]
Nijkeuter, M.; Sohne, M.; Tick, L. W.; Kamphuisen, P. W.; Kramer, M. H.; Laterveer, L.; van Houten, A. A.; Kruip, M. J.; Leebeek, F. W.; Buller, H. R.; Huisman, M. V.; Christopher Study, Investigators, The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study, Chest, 131, 2, 517-23, 2007	**Study lacks risk score stratification**
Rodriguez-Cerrillo, M.; Alvarez-Arcaya, A.; Fernandez-Diaz, E.; Fernandez-Cruz, A., A prospective study of the management of non-massive pulmonary embolism in the home, European Journal of Internal Medicine, 20, 6, 598-600, 2009	**Study lacks risk score stratification**
Santamaria, A.; Juarez, S.; Reche, A.; Gomez-Outes, A.; Martinez-Gonzalez, J.; Fontcuberta, J.; Investigators, Esfera, Low-molecular-weight heparin, bemiparin, in the outpatient treatment and secondary prophylaxis of venous thromboembolism in standard clinical practice: the ESFERA Study, International Journal of Clinical Practice, 60, 5, 518-25, 2006	**Does not contain a population of people with PE** [Does not report on PE patients]
Siragusa, S.; Arcara, C.; Malato, A.; Anastasio, R.; Valerio, M. R.; Fulfaro, F.; Lo Coco, L.; Grimaudo, S.; Bajardi, G.; Abbadessa, V.; Gebbia, N., Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients, Annals of Oncology, 16suppl4, iv136-139, 2005	**Study lacks risk score stratification**
Weeda, E. R.; Peacock, W. F.; Fermann, G. J.; Wells, P. S.; Ashton, V.; Crivera, C.; Bunz, T. J.; Wildgoose, P.; Schein, J. R.; Coleman, C. I., Outcomes associated with observation stays versus inpatient admissions for pulmonary embolism, Journal of Thrombosis & Thrombolysis, 42, 4, 513-9, 2016	**Not a relevant study design** [Retrospective study]

Observational studies excluded by the Guideline Updates Team (search update)

Study	Reason for exclusion
Actrn (2012) Early discharge of patients diagnosed with low risk pulmonary embolism from emergency departments (EDPED): a cost effectiveness study.	**Not a relevant study design** [Retrospective study]
Boucher, M, Rodger, M, Johnson, Ja et al. (2003) Shifting from inpatient to outpatient treatment of deep vein thrombosis in a tertiary care center: a cost-minimization analysis. Pharmacotherapy 23(3): 301-309	**Not a relevant study design** [Retrospective study]
Bungard, T. J., Ritchie, B., Bolt, J. et al. (2018) Anticoagulant therapies for acute venous thromboembolism: A comparison between those discharged directly from the emergency department	**Not a relevant study design** [Retrospective study]

Study	Reason for exclusion
versus hospital in two Canadian cities. BMJ Open 8 (10)	
Frank Peacock, W., Coleman, C. I., Diercks, D. B. et al. (2018) Emergency Department Discharge of Pulmonary Embolus Patients. Academic Emergency Medicine 25(9): 995-1003	**Not a relevant study design** [Retrospective study]
Hacobian, M, Shetty, R, Niles, Cm et al. (2010) Once daily enoxaparin for outpatient treatment of acute venous thromboembolism: a case-control study. Clinical and applied thrombosis/hemostasis 16(1): 21-25	**Not a relevant study design** [Retrospective study]
Kabrhel, C., Rosovsky, R., Baugh, C. et al. (2018) Multicenter Implementation of a Novel Management Protocol Increases the Outpatient Treatment of Pulmonary Embolism and Deep Vein Thrombosis. Academic Emergency Medicine.	**Not a relevant study design** [Retrospective study]
Nct (2016) Hospitalization or Out-treatment ManagEment of Patients With Pulmonary Embolism: a Randomized Controlled Trial. Https://clinicaltrials.gov/show/nct02811237	**Not a relevant study design** [Protocol only]
Vanni, S., Becattini, C., Nazerian, P. et al. (2018) Early discharge of patients with pulmonary embolism in daily clinical practice: A prospective observational study comparing clinical gestalt and clinical rules. Thrombosis Research 167: 37-43	**Not a relevant comparison**
Yoo, H. H., Nunes-Nogueira, V. S., Fortes Villas Boas, P. J. et al. (2019) Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database of Systematic Reviews 3: cd010019	**Systematic review with no new studies meeting inclusion criteria**

Appendix J – References

Included Systematic reviews

Yoo HHB, Nunes-Nogueira V, Fortes Villas Boas PJ, Broderick C. Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD010019. DOI: 10.1002/14651858.CD010019.pub3

Yoo HHB, Nunes-Nogueira VS, Fortes Villas Boas PJ, Broderick C. Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.:CD010019. DOI: 10.1002/14651858.CD010019.pub2.

Included Randomised controlled trials

Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. An international, randomized non-inferiority trial of outpatient versus inpatient treatment for pulmonary embolism. Journal of General Internal Medicine 2011;26(10):1220.

Peacock WF, Coleman CI, Diercks DB, Francis S, Kabrhel C, Keay C, et al. Emergency department discharge of pulmonary embolus patients. Academic Emergency Medicine 2018;25(9):995-1003

Excluded studies (main search)

Anonymous (1991) A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. Thrombosis & Haemostasis 65(3): 251-6

Aujesky, D., Roy, P. M., Verschuren, F. et al. (2011) Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 378(9785): 41-8

Belcaro, G., Nicolaides, A. N., Cesarone, M. R. et al. (1999) Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. Angiology 50(10): 781-7

Bledsoe, J. R., Woller, S. C., Stevens, S. M. et al. (2018) Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. Chest 154(2): 249-256

Chong, B. H., Brighton, T. A., Baker, R. I. et al. (2005) Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. Journal of Thrombosis & Thrombolysis 19(3): 173-81

Crouser, N., Malik, A. T., Jain, N. et al. (2018) Discharge to Inpatient Care Facility After Vertebroplasty/Kyphoplasty: Incidence, Risk Factors, and Postdischarge Outcomes. World Neurosurgery 118: e483-e488

Dahl, O. E., Gudmundsen, T. E., Bjornara, B. T. et al. (2003) Risk of clinical pulmonary embolism after joint surgery in patients receiving low-molecular-weight heparin prophylaxis

in hospital: a 10-year prospective register of 3,954 patients. Acta Orthopaedica Scandinavica 74(3): 299-304

Fang, M. C., Fan, D., Sung, S. H. et al. (2017) Validity of Using Inpatient and Outpatient Administrative Codes to Identify Acute Venous Thromboembolism: The CVRN VTE Study. Medical Care 55(12): e137-e143

Federman, A. D., Soones, T., DeCherrie, L. V. et al. (2018) Association of a bundled hospital-at-home and 30-day postacute transitional care program with clinical outcomes and patient experiences. JAMA Internal Medicine 178(8): 1033-1041

Huang, W., Goldberg, R. J., Anderson, F. A. et al. (2016) Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: population-based Worcester Venous Thromboembolism Study. Journal of Thrombosis & Thrombolysis 41(3): 525-38

Isene, R., Bernklev, T., Hoie, O. et al. (2014) Thromboembolism in inflammatory bowel disease: results from a prospective, population-based European inception cohort. Scandinavian Journal of Gastroenterology 49(7): 820-5

Jamal, M. H., Corcelles, R., Shimizu, H. et al. (2015) Thromboembolic events in bariatric surgery: a large multi-institutional referral center experience. Surgical Endoscopy 29(2): 376-380

Kahn, S. R., Akaberi, A., Granton, J. T. et al. (2017) Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study. American Journal of Medicine 130(8): 990.e9-990.e21

Lozano, F., Trujillo-Santos, J., Barron, M. et al. (2014) Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. Journal of Vascular Surgery 59(5): 1362-7.e1

Lui, B.; Tran, A.; Montalto, M. (2007) Treatment of patients with pulmonary embolism entirely in Hospital in the Home. Australian Family Physician 36(5): 381-4

Maestre, A., Sanchez, R., Rosa, V. et al. (2010) Clinical characteristics and outcome of inpatients versus outpatients with venous thromboembolism: findings from the RIETE Registry. European Journal of Internal Medicine 21(5): 377-82

Nijkeuter, M., Sohne, M., Tick, L. W. et al. (2007) The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study. Chest 131(2): 517-23

Otero, R., Uresandi, F., Jimenez, D. et al. (2010) Home treatment in pulmonary embolism. Thrombosis Research 126(1): e1-5

Ozcan Cetin, E. H., Cetin, M. S., Canpolat, U. et al. (2017) Platelet-to-lymphocyte ratio as a novel marker of in-hospital and long-term adverse outcomes among patients with acute pulmonary embolism: A single center large-scale study. Thrombosis Research 150: 33-40

Rodriguez-Cerrillo, M., Alvarez-Arcaya, A., Fernandez-Diaz, E. et al. (2009) A prospective study of the management of non-massive pulmonary embolism in the home. European Journal of Internal Medicine 20(6): 598-600

Santamaria, A., Juarez, S., Reche, A. et al. (2006) Low-molecular-weight heparin, bemiparin, in the outpatient treatment and secondary prophylaxis of venous thromboembolism in standard clinical practice: the ESFERA Study. International Journal of Clinical Practice 60(5): 518-25

Siragusa, S., Arcara, C., Malato, A. et al. (2005) Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. Annals of Oncology 16suppl4: iv136-139

Stewart, M., Bledsoe, J., Madsen, T. et al. (2015) Utilization and Safety of a Pulmonary Embolism Treatment Protocol in an Emergency Department Observation Unit. Critical Pathways in Cardiology: A Journal of Evidence-Based Medicine 14(3): 87-9

Weeda, E. R., Peacock, W. F., Fermann, G. J. et al. (2016) Outcomes associated with observation stays versus inpatient admissions for pulmonary embolism. Journal of Thrombosis & Thrombolysis 42(4): 513-9

Zondag, W., den Exter, P. L., Crobach, M. J. et al. (2013) Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis & Haemostasis 109(1): 47-52

Zondag, W., Hiddinga, B. I., Crobach, M. J. et al. (2013) Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 41(3): 588-92

Zondag, W., Vingerhoets, L. M., Durian, M. F. et al. (2013) Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis & Haemostasis 11(4): 686-92

Excluded studies (search update)

Actrn (2012) Early discharge of patients diagnosed with low risk pulmonary embolism from emergency departments (EDPED): a cost effectiveness study.

Boucher, M, Rodger, M, Johnson, Ja et al. (2003) Shifting from inpatient to outpatient treatment of deep vein thrombosis in a tertiary care center: a cost-minimization analysis. Pharmacotherapy 23(3): 301-309

Bungard, T. J., Ritchie, B., Bolt, J. et al. (2018) Anticoagulant therapies for acute venous thromboembolism: A comparison between those discharged directly from the emergency department versus hospital in two Canadian cities. BMJ Open 8 (10)

Frank Peacock, W., Coleman, C. I., Diercks, D. B. et al. (2018) Emergency Department Discharge of Pulmonary Embolus Patients. Academic Emergency Medicine 25(9): 995-1003

Hacobian, M, Shetty, R, Niles, Cm et al. (2010) Once daily enoxaparin for outpatient treatment of acute venous thromboembolism: a case-control study. Clinical and applied thrombosis/hemostasis 16(1): 21-25

Kabrhel, C., Rosovsky, R., Baugh, C. et al. (2018) Multicenter Implementation of a Novel Management Protocol Increases the Outpatient Treatment of Pulmonary Embolism and Deep Vein Thrombosis. Academic Emergency Medicine.

Nct (2016) Hospitalization or Out-treatment ManagEment of Patients With Pulmonary Embolism: a Randomized Controlled Trial. Https://clinicaltrials.gov/show/nct02811237

Vanni, S., Becattini, C., Nazerian, P. et al. (2018) Early discharge of patients with pulmonary embolism in daily clinical practice: A prospective observational study comparing clinical gestalt and clinical rules. Thrombosis Research 167: 37-43

Yoo, H. H., Nunes-Nogueira, V. S., Fortes Villas Boas, P. J. et al. (2019) Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database of Systematic Reviews 3: cd010019