
Article:
Horner, D., Pandor, A., Goodacre, S. orcid.org/0000-0003-0803-8444 et al. (2 more authors) (2018) Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilisation due to injury: a systematic review. Journal of Thrombosis and Haemostasis. ISSN 1538-7933

https://doi.org/10.1111/jth.14367

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Article type : Original Article - Clinical Haemostasis and Thrombosis

Title:

Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilisation due to injury: a systematic review

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Essentials

- Thromboprophylaxis after lower limb injury is often based on complex risk stratification.
- Our systematic review identified variables predicting venous thromboembolism (VTE) in this group.
- Age and injury type were commonly reported to increase the odds of VTE (Odds Ratio 1.5 to 3.48).
- We found limited evidence to support the use of other risk factors within prediction models.

Summary

Background

Patients immobilised after lower limb injury are at risk of venous thromboembolism (VTE). There is international variation in the use of thromboprophylaxis for such patients. Risk based strategies have been adopted to aid decision making in many settings. The accuracy of these strategies is unclear.

Objectives

A systematic review was undertaken to identify all individual patient identifiable risk factors linked to any VTE outcome following lower limb immobilisation.

Methods

Several electronic databases were searched from inception to May 2017. Any studies which included a measurement of VTE patient outcome in adults requiring temporary immobilisation (e.g. leg cast or brace in an ambulatory setting) for an isolated lower limb injury and reported risk factor variables were included. Descriptive statistics and thematic analysis were used to synthesise the evidence.

Results

Our database search returned 4771 citations, of which 15 studies reporting outcome data on 80,678 patients were eligible for analysis. Risk factor associations were reported through regression analyses, non-parametric tests and descriptive statistics. All studies were assessed as at moderate or serious risk of bias using the ROBINS-I risk of bias tool.

Advancing age and injury type were the only individual risk factors demonstrating a reproducible association with increased symptomatic and/or asymptomatic VTE rates. Several risk factors currently used in scoring tools did not appear to be robustly evaluated for subsequent association with VTE, within these studies.

Conclusions

Clinicians should be aware of the limited evidence to support individual risk factors in guiding thromboprophylaxis use for this patient cohort.

Summary (Additional)

Funding

This study was funded by the United Kingdom National Institute for Health Research Health Technology Assessment Programme (project number 15/187/06).

PROSPERO Registration

Pandor A, Goodacre S, Horner D, Stevens JW, Clowes M, Davis S, Stevenson M. Systematic review and cost-effectiveness analysis of thromboprophylaxis for lower limb immobilisation. PROSPERO 2017 CRD42017058688. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017058688

Keywords

Risk

Immobilization

Venous thromboembolism

Casts, surgical

BACKGROUND

Venous thromboembolic (VTE) disease is a major global cause of morbidity and mortality.[1, 2] An estimated 10 million episodes are diagnosed yearly; over half of these episodes are provoked by hospital admission or procedure and result in significant loss of disability adjusted life years.[3] As a result, there has been sustained focus on prevention over the last two decades.[4-6] However, there are still patient groups where the balance of benefit and risk from thromboprophylaxis remains unclear.

Outpatients placed in temporary lower limb immobilisation following injury are one such cohort. Approximately 70,000 such patients are discharged from UK emergency departments each year, with an overall symptomatic VTE rate approaching 2%.[7-9] Some of these events are fatal, leading to natural reflection on prevention strategies and occasional coronial recommendations.[10, 11] Wide variation in practice regarding the use of immobilisation (plaster cast, hinged brace or protective boot) and the use of thromboprophylaxis continues for these patients.[12-14] International guidance offers conflicting advice, from no intervention, through pragmatic shared decision making all the way up to *routine* pharmacological thromboprophylaxis.[7, 15, 16] This lack of consensus fosters clinical uncertainty.

The low symptomatic VTE event rate, financial implications, opportunity costs and clinical risks of therapy may be cited as reasons to avoid routine thromboprophylaxis. There are several studies which also suggest that in cohorts without overt additional risk factors, the incidence of clinically relevant VTE in immobilised ambulatory patients is negligible.[13, 17] As such, recent evidence has begun to focus on discrimination through scoring systems and risk assessment models, to promote tailored thromboprophylaxis to those most likely to benefit.[18] Most scores focus on risk factors relevant to inpatients; it is plausible that these same risk factors increase the likelihood of VTE in ambulatory patients with lower limb immobilisation, but this has not been formally evaluated.

Despite publication of three risk assessment methods for this particular population in the last decade, the derivation and validation of these scoring systems is often unclear.[7, 18, 19] Included risk factors are often double counted, attributed 'points' in a seemingly arbitrary fashion and dichotomised without evidential support. In addition, it is unclear whether these scores are designed to detect all VTE; eighty percent of deep vein thrombosis (DVT) can be clinically silent initially, a statistic that perhaps explains embolisation accounting for 30% of first VTE presentations.[20] The validity of scoring systems and risk factors therefore vary depending on the use of routine ultrasound to screen for silent DVT as an outcome, or investigation only of those patients with concerning clinical symptoms.

We sought to identify which individual risk factors have been identified within the literature as likely to increase the risk of both asymptomatic and symptomatic VTE in patients with temporary lower limb immobilisation. We then looked to compare these identified risk factors to those highlighted within published risk prediction tools, such as the Guidelines in Emergency Medicine Network (GEMNet), Plymouth and Leiden Thrombosis Risk in Plaster-cast (L-TRiP-cast) rules.[7, 18, 19]

METHODS

The systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[21] This review was part of a larger project on thromboprophylaxis for lower limb immobilisation which was

registered on the PROSPERO international prospective register of systematic reviews (CRD42017058688). The full protocol is available here.

Data sources and search strategy

Potentially relevant studies were identified through searches of ten electronic databases including MEDLINE (1946 to May 2017), EMBASE (1974 to May 2017), and the Cochrane Library (2017, issue 4). The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (e.g. venous thromboembolism in people with lower limb immobilisation) with risk factor assessment or risk prediction modelling terms (used in the searches of MEDLINE, Cochrane Library and EMBASE only). Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), performing a citation search of relevant articles, contacting key experts in the field and undertaking systematic keyword searches of the World Wide Web using the Google search engine. No language or date restrictions were used on any database. Further details on the search strategy can be found in **Table S1** (supporting information).

Study selection

All titles were examined for inclusion by one reviewer (AP) and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to venous thromboembolism) were excluded. All abstracts and full text articles were then examined independently by two reviewers (AP and DH). Any disagreements in the selection process were resolved through discussion with a third reviewer (SG) and included by consensus.

Studies were considered eligible for inclusion if they met the following criteria: a) any study design which included a measurement of VTE patient outcome (symptomatic and/or asymptomatic); b) adults (age over 16 years) requiring temporary immobilisation (e.g. leg cast or brace in an ambulatory setting) for an isolated lower limb injury c) any studies that reported and analysed data on individual risk factors associated with deep vein thrombosis or pulmonary embolism.

Data extraction and quality assessment

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (AP) into a standardised data extraction form and independently checked for accuracy by a second (DH). Any discrepancies were resolved through discussion to achieve agreement. Where differences were unresolved, a third reviewer's opinion was sought (SG).

The methodological quality of each included study was assessed using the Risk Of Bias In Non-randomized Studies - of Interventions tool (ROBINS-I, formerly called A Cochrane Risk of Bias Assessment Tool - for Non-Randomized Studies of Interventions, ACROBAT-NRSI).[22] The tool is based on the original Cochrane risk of bias tool for randomised studies [23] and also builds on related tools such as QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies).[24] ROBINS-I[22] provides a detailed framework for assessment and judgement of risk of bias domains, and has been used previously within the systematic review literature.[25]

All studies were analysed using this tool[22] regardless of whether the original study design included randomisation to other exposures, thus ensuring that risk of bias was assessed specifically for the comparisons of interest to this review. It is important to note that the quality assessment reflects how well a specific result evaluated the association of interest to this review, regardless of the objectives of the original study.

Data synthesis and analysis

We considered VTE to comprise any subsequent recorded diagnosis of asymptomatic or symptomatic deep vein thrombosis, pulmonary embolism or death attributable to either pathology. We made no attempt to distinguish between anatomical location, thrombus burden or clinical sequelae of VTE for this project, in accordance with the definitions of hospital acquired thrombosis produced by NHS England (any VTE occurring during hospital admission or up to 90 days after admission).[26] Individual risk factors highlighted through regression, odds ratio analysis or parametric testing as being significantly associated with an increased, or decreased likelihood of subsequent VTE were extracted. In particular, we searched each paper for evidence of individual risk factors highlighted within current risk stratification tools and recorded their prediction performance when addressed. Other risk factors demonstrating an association with asymptomatic or symptomatic VTE in the context of individual studies were

also reported. We were unable to perform meta-analysis due to significant levels of heterogeneity between studies, variable reporting items and the high risk of attributable bias. Descriptive statistics and thematic analysis were used to synthesise risk factors acting in a reproducible fashion across studies. All analyses were conducted using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Figure 1 summarises the process of identifying and selecting relevant literature. Of 4771 citations, 75 full text articles were retrieved and fully assessed; 15 of these studies met all inclusion criteria.[27-41] A list of the 60 excluded studies following full text review, with reasons for exclusion, is presented in **Table S2**.

The design and patient characteristics of the included studies[27-41] are summarised in **Table 1.** All studies were published between 1993 and 2017. Five were RCTs with conservative arms,[27, 28, 32, 33, 41] three were prospective observational cohort or cross-sectional studies,[30, 35, 38] one was a case-control study[39] and six were retrospective cohort studies)[29, 31, 34, 36, 37, 40], conducted in ten different countries (Australia,[29, 30, 36] Canada,[28, 34] China,[41] Denmark,[40] France,[38] Germany,[27, 32, 33] Iran,[35] the Netherlands,[39] the UK[31] and the USA).[37] The vast majority of the studies (n=11) were entirely outpatient based,[27-33, 35, 36, 38, 41] whereas the remaining studies[34, 37, 39, 40] included patients with a short duration inpatient stay to facilitate day case surgery. In total, data were collated on 80,678 patients with a subsequent reported outcome of VTE positive or negative following temporary lower limb immobilisation. The median prevalence of any VTE from the studies was 4.8% (ranging from 0.22%[31] to 23.5%[34]) and the mean age ranged from 33.8 years[32] to 52.6 years[40]. The proportion of male subjects ranged from 45.8%[30] to 86.1%,[34] with a median across the studies of 56.3%. The median prevalence of **symptomatic VTE only** across all studies with interpretable outcome data (77,261 patients) was 2.9%.

The duration of follow up varied between studies. Ten studies reported follow up over a period of at least three months[28-31, 34, 37-41] and one study followed up patients up to 14 days.[35] Although four studies failed to record the duration of follow up,[27, 32, 33, 36] two of these appeared to report follow up only for the duration of the plaster cast, which averaged 15.7 days[33] and 17 days[32] respectively. Eight studies collected data on risk factors prospectively via physician assessment or questionnaire,[27, 28, 30, 32, 33, 38, 39, 41] six studies collected this data through clinical records, electronic patient notes or registry information.[29, 31, 34, 36, 37, 40] One study did not report the methodology for this aspect of data collection.[35] Analysis and methodology of VTE diagnosis subsequent to immobilisation varied between studies, including prospective screening in all patients following plaster removal (seven studies),[27, 28, 30, 32, 33, 35, 41] adjudicated diagnostic evaluation in those with symptoms (two studies)[38, 39] and retrospective identification of VTE through interrogation of clinical records/health databases (six studies).[29, 31, 34, 36, 37, 40] A single study[31] looked only at the subsequent diagnosis of pulmonary embolism as an outcome, with predictably reduced prevalence. The association of individual risk factors with subsequent VTE was assessed through regression analyses (nine studies),[28, 29, 31, 36-41] non-parametric tests (two studies)[30, 34] and descriptive statistics (four studies).[27, 32, 33, 35]

The overall methodological quality of the 15 included studies is summarised in **Figure 2** and **Table 2**. All studies were deemed to be at overall moderate (seven studies)[27, 28, 32, 33, 37, 40, 41] or serious (eight studies)[29-31, 34-36, 38, 39] risk of bias, using the ROBINS-I[22] framework for assessment and judgement. Studies scoring at serious risk of bias did so predominately on selection of participants into the study, perhaps highlighting the issue with retrospective observational work into VTE outcomes; patients deemed to be at high risk in these cohorts are often individually treated with thromboprophylaxis (as highlighted in **Table 1**), or managed in a different manner to other patients, thus reducing the overall reported risk in the population.

Age was the most consistent individual risk prediction factor for any VTE outcome, highlighted across eleven studies.[28, 30, 32-34, 36-41] Odds ratios reported for age varied from 1.05[41] to 3.48[36] with limited estimates of precision. Injury type as a risk factor was highlighted across six studies,[28, 32, 33, 36, 38, 39] all using multivariate logistic regression to suggest that severe traumatic injuries and fractures (when compared to soft tissue injuries) were independently associated with increased risk of VTE. Body mass index (BMI) was the third most

consistent individual risk highlighted, noted as independently predictive of VTE across four studies [33, 39-41] with odds ratios ranging from 1.2[41] to 17.2.[39] However, six studies looked for and found no association between BMI and subsequent VTE. [30, 32, 34, 37, 38, 42]

Both age and BMI feature in the published and most widely used risk prediction models. Injury type and severity is featured in the L-TRIP and Plymouth score, but not incorporated within the GEMNET guideline as an individual feature. All individual risk factors currently used within the above risk stratification tools and their reported association with VTE across all included studies, are shown in **Table 3**. Despite being present within several risk stratification tools, pregnancy, recent hospital admission and preceding immobility as individual characteristics were not identified and prospectively/retrospectively assessed by any of the included studies. As such, these risk factors do not appear to have been evaluated in the literature regarding association with subsequent VTE, in patients with temporary lower limb immobilisation after injury.

We found similar results when an outcome of **symptomatic VTE only** was used within studies. In addition, we performed a post-hoc analysis excluding studies with less than 90 days follow up, or excluding studies at high risk of bias. Age continued to be a consistent predictor of VTE risk, highlighted in 8/10 studies and 6/7 studies, respectively. The results of these exclusions on other risk factor variables are presented in **tables S3 and S4**.

We found few other individual risk factors in this study not included in current scoring systems, but associated with subsequent development of VTE after lower limb immobilisation. These included recent air travel (one study),[29] coagulopathy and peripheral arterial disease (one study).[40] A single paper looked at the cumulative incidence of clinical risk factors per patient and reported the presence of three or more factors to be significantly associated with development of VTE.[35]

Methodology of reporting individual variables to have no association with subsequent VTE was inconsistent and heterogeneous. Six studies reported no association between gender and VTE;[28, 30-32, 36, 39] five studies reported no association between exogenous oestrogen use and VTE;[30, 32-34, 42] six studies reported no association between smoking and subsequent

VTE.[30, 32, 34, 38, 42, 43] Several papers produced conflicting results; six studies reported no association between raised BMI and subsequent risk of VTE [30, 32, 34, 37, 38, 42] and one study reported no association with increasing age.[31] These other identified risk factors and all negative associations are reported in **Table 4.**

DISCUSSION

In this systematic review of risk factors associated with VTE following temporary lower limb immobilisation after injury, we found that only advancing age was consistently highlighted as a risk factor for VTE across the majority of included studies. Injury type showed weaker association, with consistent association across six studies. All studies were deemed to be at moderate or serious risk of bias overall following structured quality assessment. These findings raise questions regarding the reliability of using individual risk factors to determine subsequent VTE risk in this cohort.

Our study is the first systematic review to assess the link between individual risk factors and all VTE i.e. symptomatic and/or asymptomatic following temporary lower limb immobilisation after injury. This is an important distinction, as our population of interest differs from generic thrombosis datasets; patients with lower limb injury are potentially younger, more active and devoid of comorbidity than those presenting with other forms of VTE.[44] Our study was conducted with robust methodology and was undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination. [45] The protocol was registered in advance with PROSPERO. Clinical experts were involved throughout to assess the validity and applicability of research during the project. We reported descriptive statistics to provide plain insight into the limited evidence base applicable to the subject matter, and the scientific concerns regarding validity of the data.

Our systematic review returned data from randomised controlled trials, prospective cohorts and retrospective health database registries. As such, we were unable to combine data for additional analysis of risk or consider performing an individual patient data meta-analysis. Despite strict inclusion criteria, the included studies also demonstrated high levels of heterogeneity.

Several studies included patients receiving operative intervention and short inpatient stays. Following the introduction of guidance on thromboprophylaxis to reduce the risk of hospital acquired thrombosis, it is reasonable to assume that in a modern healthcare environment most of these patients would receive routine thromboprophylaxis.[46] As such, inclusion of these patients could lead to false reassurance regarding low incidence of VTE. However, we considered patients with a short inpatient stay (<5 days) to fit within our scope of interest; initial thromboprophylaxis in hospital may be inadequate in dose and/or duration, and these patients often remain temporarily immobilised for a period of 4-8 weeks in total. Debate also persists about the type and duration of thromboprophylaxis in this setting. Outside randomised trial data, there was significant heterogeneity in thromboprophylaxis regimens by agent, dose and duration. As such, observational cohort studies attempting to link individual risk factors at baseline to subsequent VTE diagnosis are at risk of confounding and selection bias. In addition, some of the larger datasets reported VTE rates related to risk factors without ascertaining which, if any patients, had received prophylaxis. This is a core issue surrounding this topic; definitive VTE event rates, associated risk factors and adverse events cannot be accurately determined by studying a group of patients, however large, in which clinicians have selected higher risk candidates to receive any form of prophylaxis.

Our definition of VTE also masked any subgroup analysis by anatomical location. As such, we were unable to comment on clot burden or whether subsequent VTE occurred in the injured/immobilised limb. While this latter point is perhaps intuitive, there is additional direct clinical relevance to this question; if VTE is more likely to occur in the affected limb, this suggests a focal issue from a more generalised prothrombotic state and that modification of treatment plans/immobilisation strategies could be more beneficial than generic prophylaxis.

All the studies within our review were classed as at moderate or severe risk of bias. As such, any conclusions regarding the influence of risk factors on the subsequent development of VTE drawn are based on weak evidence and have the potential to be inaccurate. In addition, several studies individually report a lack of power to accurately discriminate whether an individual risk factor was not associated with VTE, or whether the sample size precluded statistical association. As such, a lack of significant association within a study cannot be interpreted as direct evidence against the individual risk factor, without further detailed scrutiny.

This is the first systematic review conducted to look directly at individual risk factors increasing the risk of VTE in patients with lower limb injury and immobilisation, discharged to an outpatient setting. Previous work has attempted to address a similar issue in patients undergoing elective foot and ankle surgery.[47-49] We consider this to be a different population due to the pathological differences between blunt forced and surgical trauma, expert image guided reduction and postoperative immobilisation regimes.

Advancing age has long been recognised as an established risk for VTE. [50] Our findings support this as one of the more reliable individual risk factors consistently demonstrating association with the likelihood of subsequent VTE. Causation within this study cannot be determined due to variable methodology. Indeed, our demonstration of advancing age as a consistent individual risk factor for VTE may probably reflects the increasing prothrombotic state seen with ageing, irrespective of immobilisation. Although we found conflicting evidence on increasing BMI as a risk factor for VTE within this specific cohort of patients, this issue has similar face validity. Increased risk is thought to be related to the prothrombotic state induced by adipocytes and potential reduction in venous flow through larger veins.[51, 52]

The hypothesis that extent of injury acts as a predictor of VTE risk is in keeping with those studies which report a low VTE incidence in patients with immobilisation following soft tissue injury.[38] In addition, there is face validity to the idea of a more severe injury leading to inflammatory cytokines, prothrombotic changes, endothelial activation and subsequent increased predisposition to VTE, in keeping with Virchow's triad. However, the challenge remains of decoupling the extent of injury from the type of immobilisation; patients with severe fracture patterns are more likely to be placed in stricter and more extensive immobilisation. Lastly, we found only two studies identifying cumulative risk with an increased incidence of VTE. [39, 53] While this is perhaps intuitive, the supporting data appears limited. This could be confounded by exclusion criteria for high risk patients within the trials, or the use of thromboprophylaxis for patients with multiple risk factors within observational studies. We did not look to validate the performance of any proposed risk models within this study.

There are no previous systematic reviews on this topic to which our work can be compared. However, several large registries have been recently interrogated in attempt to derive robust prediction rules for this population, albeit with some methodological concerns. The most recent

is the L-TRiP cast rule, derived from a large population-based case control study of over 10,000 cases, including 4446 VTE patients.[18] During this study, the authors performed univariate analysis on 54 candidate predictor variables in attempt to derive a full, restricted and clinical decision rule for use in this population. Age and BMI featured in all 3 models, with odds ratios reported on univariate analysis of 3.2 (95% CI 2.9 to 3.6) for age ≥55 and 3.1 (95% CI 2.5 to 3.9) for BMI ≥35 respectively. No specific candidate variable in this study referred to injury type. However, the extent of immobilisation was specifically assessed as a predictor, with odds ratios of 10.7 (95% CI 4.3 to 26.6) and 8.7 (95% CI 5.5 to 13.7) for complete leg and lower leg casts respectively, when compared to no cast immobilisation. These latter findings perhaps serve as a proxy marker of injury severity, and the association with VTE.

The results from the L-TRiP study are in keeping with this systematic review, although it should be noted that the highest performing individual risk factor on univariate analysis within the L-TRiP cohort was use of tamoxifen with an odds ratio of 11.6 (95% CI 3.3 to 41.2). We found no evidence from other studies that would support this grade of association.

The findings from this systematic review suggest that while common generic predictors of risk for VTE are relevant to the cohort of interest, there is little consistency within the literature regarding the value of other candidate variables. In addition, there is poor evidence to support the theory of cumulative risk and the existing literature is marred by moderate to serious risk of bias. Our work therefore raises questions regarding the validity of current prediction rules in clinical use created by expert consensus, without robust external validation. There is a pressing need for prospective validation studies in the appropriate cohort of patients to assess the sensitivity and specificity of these rules. Complex scoring systems should also be compared to those which select patients for thromboprophylaxis on the basis of individual strong generic risks (such as advancing age and severe injury), or clinician gestalt.

Our quality assessment overview highlights the limitations of the current literature. As such there remains a role for further high quality prospective observational cohort studies on this topic, particularly looking at the rarer but more severe VTE risks. This research could include pregnant women, those with high risk thrombophilia and those using exogenous oestrogens. However, such research will have challenges in a health system with national guidance prompting consideration of risk and bespoke prescribing.[7, 46] In addition, the low frequency

of events may result in real difficulty obtaining valid datasets. Such studies would need careful assessment of baseline risk, transparent reporting of thromboprophylaxis and an independently adjudicated, patient-centred outcome measure.

CONCLUSIONS

We found that increasing age and injury severity only, were the individual risk factors most consistently associated with VTE following lower limb immobilisation after acute injury. All studies included in the review were deemed at moderate or serious risk of bias. Clinicians should be aware of the limited evidence to support individual risk factors in guiding thromboprophylaxis use for this patient cohort.

Authorship statement

D. Horner, A. Pandor, B. Hunt and S. Goodacre were responsible for identifying the research question, obtaining funding and drafting of the initial protocol. A. Pandor and M. Clowes were responsible for the relevant literature searches and assistance with sifting of results. D. Horner and A. Pandor were responsible for the drafting of this paper, although all authors provided comments on the drafts and read and approved the final version. D. Horner is the guarantor for the paper.

Acknowledgements

The authors would like to thank all additional members of the core project group for HTA 15/187/06, including Dr Kerstin Hogg, Dr Tim Nokes and Mr Jon Keenan for their input and commentary throughout the work. We are also indebted to Joanne Hinde for assistance with logistics and administration.

This study was funded by the United Kingdom National Institute for Health Research Health Technology Assessment Programme (project number 15/187/06). The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors. The funders had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication

Disclosure of Conflict of Interests

On behalf of all authors, I declare no known conflict of interest to exist regarding this research article.

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Figure Legends:

Figure 1: Flow chart of abstract screening, exclusion and final selection

Figure 2: ROBINS-I risk of bias assessment graph

Table Legends:

Table 1: Study Design and Patient Characteristics of included articles

Table 2: Quality Assessment Overview

Table 3: Identified individual risk factors and their association with developing VTE

Table 4: Other Identified individual risk factors, their association with developing VTE and narrative review.

Table S1: Literature search strategies

Table S2: Excluded studies following full text review

Table S3: Individual risk factors and their reported strength of association with developing VTE (Excluding studies with F/up <90 days)

Table S4: Individual risk factors and their reported strength of association with developing VTE (Excluding studies at high risk of bias)

Table 1: Summary of design and patient characteristics - Review of individual risk factors associated with VTE risk

Author year, country	Design, setting	Inclusion criteria (main)	Patients, sex, age (years)	Incidence of VTE	Prophylaxis	Duration of follow-up	Risk factor ascertainment	Outcome ascertainment	Statistical analysis
Gehling *et al.,* 1998; Germany	Design: Prospective open-label RCT Setting: Outpatient	Age >16 years with lower limb injury requiring immobilisation with plaster or bandages (and at least one risk factor for VTE)	N=287 50.5% male Mean age: 36.3[a]	LMWH group: 6.3% Aspirin group: 4.8%	NR	NR	Physician assessment (prospective)	Clinical assessment, screening sonography and confirmation phlebography	NR (appears descriptive)
Goel *et al.,* 2009; Canada	Design: Prospective double-blind RCT Setting: Outpatient	Adults 18 to 75 years with unilateral displaced fractures below the knee requiring operative intervention	N=238 62% male Mean age: 40.5[a]	LMWH group: 8.7% Control group: 12.6%	No prophylaxis prior to randomisation	Minimum of 3 months following surgery or until the fracture had united.	Physician assessment (prospective)	Clinical assessment and bilateral lower leg venography for all patients	Univariate and multivariate logistic regression
Kock *et al.,* 1995; Germany	Design: Prospective open-label RCT Setting: Outpatient	Adults 18 to 65 years undergoing conservative treatment for below knee injury with cylinder or below knee cast	N=339 61% male Mean age: 33.8[a]	LMWH group: 0% Control group: 4.3%	No prophylaxis prior to randomisation	NR (however, duration of casting: LMWH group, 15.2 days; Control group, 18.8 days)	Physician assessment (prospective)	Clinical assessment, screening sonography and confirmation phlebography	NR (appears descriptive)
Kujath *et al.,* 1993; Germany	Design: Prospective open-label RCT Setting: Outpatient	Age >16 years undergoing conservative treatment for lower limb injury with below knee plaster applied for	N=253 58% male Mean age: 34.3[a]	LMWH group: 4.8% Control group: 16.5%	No prophylaxis prior to randomisation	NR (however, duration of casting: LMWH group, 15.6 days; Control	Physician assessment (prospective)	Compression ultrasound by 2 examiners and confirmatio	NR (appears descriptive)

		>7 days				group, 15.8 days)		n phlebography	
Zheng *et al.,* 2017; China	Design: Prospective double-blind RCT Setting: Outpatient	Adults >18 years with any fracture of the lower limb requiring operative treatment	N=814 62.3% male Mean age: 47.8	LMWH group: 1.5% Control group: 3.2%	No prophylaxis prior to randomisation	3 months	Physician assessment (prospective)	Blinded bilateral Doppler compression ultrasound	Logistic regression
Riou *et al.,* 2007; France	Design: Prospective cohort study Setting: Outpatient	Age >18 years with isolated lower limb injury (below the knee) managed conservatively (immobilisation duration >7 days)	N=2761 51% male Mean age: 40	6.4%	Antithrombotic prophylaxis was given to 61% patients	3 months	Physician assessment (prospective)	Adjudication committee	Logistic regression with propensity score analysis
Hanslow *et al.,* 2006; Australia	Design: Retrospective cohort study Setting: Outpatient	Patients who had an operative intervention to the foot or ankle	N=602 52% male Mean age: 42.9	5.3%	Antithrombotic prophylaxis was given to 31% patients	4.4 months	Collected from clinical records (retrospective)	Case note search, including hospital re-attendance and diagnostic imaging	Logistic regression
Jameson *et al.,* 2014; UK	Design: Retrospective cohort study Setting: Outpatient	Patients with isolated unilateral closed ankle fracture managed conservatively	N=14,777 47% male Mean age: 46.4	0.22% (PE only)	No data recorded	3 months	NR; assumed collected from clinical records (retrospective)	Inpatient mortality or coded diagnosis of pulmonary embolism within 90 days of injury	Logistic regression
Makhdom *et al.,* 2013; Canada	Design: Retrospective cohort study	All patients undergoing Achilles tendon	N=115 86.1% male Mean age:	23.5%	No peri- or post-operative	3 months	Collected from electronic	Case note search, including	Non-parametric testing using Fishers exact

	Setting: Outpatient until surgery, short day-case stay thereafter	repair	41		prophylaxis		medical record system (retrospective)	hospital re-attendance and diagnostic imaging	
Meek and Tong, 2012; Australia	Design: Retrospective cohort study Setting: Outpatient	Age >18 years with acute lower limb injury requiring temporary immobilisation (ED discharge within 24 hours of presentation)	N=1231 56.3% male Mean age: 37	2.9%	No prophylaxis (excluded if received at any dose)	NR	Electronic notes screened for eligibility by one investigator (retrospective)	Case note search, including hospital re-attendance and diagnostic imaging	Logistic regression
Patel *et al.,* 2012; USA	Design: Retrospective cohort study Setting: Mostly outpatient, some with short inpatient stays (<3 days)	All patients who had Achilles tendon rupture	N=1172 NR Mean age: 45	0.77%	Nil routine, assumed to be none provided	3 months	Collected from electronic medical record system (retrospective)	Case note search, including hospital re-attendance and diagnostic imaging	Logistic regression
Wahlsten *et al.,* 2015; Denmark	Design: Retrospective cohort study Setting: Inpatient or outpatient	Age >18 years undergoing an operative procedure for a fracture of the foot, ankle, tibia or patella	N=57,619 51.4% male Mean age: 52.6[a]	1.0%	Routine perioperative prophylaxis with nil post-operative	180 days	Collected from 5 different cross linked registries (retrospective)	Case note search, including hospital re-attendance and diagnostic imaging	Multivariate cox regression
van Adrichem *et al.,* 2014; The Netherlands	Design: Case-control study Setting:	Age 18 to 70 years with a first VTE identified at an anticoagulation clinic (cases)	N= 10,567[b] Sex: NR Mean age: NR	NR	No data recorded	3 months	Participant completed questionnaire (prospective collection)	Case note search, including hospital re-attendance	Logistic regression

	Mostly outpatient, some with short inpatient stays (<3 days)	Control group identified by random dialling method (matched for sex and age)						and diagnostic imaging	
Ho and Omari, 2017; Australia	Design: Cross-sectional study Setting: Outpatient	Age >18 years with fracture to foot/ ankle with conservative management	N=72 45.8% male Mean age: NR (median: 38)	11%	Nil routine, assumed to be none provided	6 months	Questionnaire (unclear if physician or patient completed)	Prospective compression ultrasound	Parametric and non-parametric testing with bootstrapping
Manafi Rasi *et al.,* 2012; Iran	Design: Cross-sectional study Setting: Outpatient	Age >15 years with stable foot/ ankle fracture or grade 3 sprain (non-surgical treatment)	N=95 77.9% male Mean age: 38	3%	NR	7 to 14 days	NR	Compression ultrasound by 2 independent examiners	NR (appears descriptive)

ED, Emergency Department; LMWH, low molecular weight heparin; NR, not reported; RCT, randomised controlled trial; VTE, venous thromboembolism

[a] Data calculated based on mean of means
[b] Sample included 4418 cases and 6149 controls (of these only 227 cases and 76 controls had lower extremity injuries)

Table 2: ROBINS-I risk of bias assessment summary: Review authors' judgements about each methodological quality item for each included study - Review of individual risk factors associated with VTE risk

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification/ measurement of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall[a]
Gehling *et al.,* 1998	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
Goel *et al.,* 2009	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	MODERATE
Kock *et al.,* 1995	LOW	LOW	MODERATE	MODERATE	LOW	MODERATE	MODERATE	MODERATE
Kujath *et al.,* 1993	LOW	LOW	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
Zheng *et al.,* 2017	LOW	MODERATE	LOW	LOW	MODERATE	LOW	MODERATE	MODERATE
Riou *et al.,* 2007	MODERATE	MODERATE	MODERATE	SERIOUS	MODERATE	MODERATE	MODERATE	SERIOUS
Hanslow *et al.,* 2006	MODERATE	MODERATE	MODERATE	SERIOUS	MODERATE	MODERATE	MODERATE	SERIOUS
Jameson *et al.,* 2014	MODERATE	SERIOUS	MODERATE	SERIOUS	MODERATE	MODERATE	MODERATE	SERIOUS
Makhdom *et al.,* 2013	SERIOUS	SERIOUS	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	SERIOUS
Meek and Tong, 2012	MODERATE	SERIOUS	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	SERIOUS
Patel *et al.,* 2012	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
Wahlsten *et al.,* 2015	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
van Adrichem *et al.,* 2014	MODERATE	SERIOUS	SERIOUS	SERIOUS	MODERATE	MODERATE	MODERATE	SERIOUS
Ho and Omari, 2017	SERIOUS	SERIOUS	MODERATE	MODERATE	SERIOUS	MODERATE	MODERATE	SERIOUS
Manafi Rasi *et al.,* 2012	SERIOUS	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	SERIOUS

[a] Overall risk of bias judgement (equal to the most severe level of bias found in any domain) were judged as: 1) Low risk of bias - study comparable to a well-performed randomised trial 2) Moderate risk of bias -sound for a non-randomised study but not comparable to a rigorous randomised trial 3) Serious risk of bias - the study has some important problems 4) Critical risk of bias - too problematic to provide any useful evidence on the effects of intervention

Table 3: Individual risk factors and their reported strength of association with developing VTE

Study	Risk factors associated with developing VTE														
	Permanent (present before episode of lower limb immobilisation)												**Transient** (during injured period)		
	Age	**BMI**	**Active cancer**	**Pregnancy**	**Smoking**	**Varicos-ities**	**Prior or family history of VTE**	**Significant co-morbidity**	**Known thrombo-philia**	**Exogenous oestrogen therapy**	**Recent hospital admission or surgery**	**Preceding immobility**	**Injury type**	**Immobil-isation type**	**Weight bearing status**
USING AN ENDPOINT OF ASYMPTOMATIC VTE, DETECTED BY ROUTINE SCREENING															
Gehling *et al.*, 1998	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Goel *et al.*, 2009	PSAR[a]	NSAR[a]	NSAR[a]	N/A	NSAR[a]	N/A	N/A	NSAR[a]	NSAR[a]	NSAR[a]	N/A	N/A	PSAR[a]	N/A	N/A
Kock *et al.*, 1995	PSAR[b]	NSAR[b]	N/A	N/A	NSAR[b]	NSAR[b]	N/A	N/A	N/A	NSAR[b]	N/A	N/A	PSAR[b]	PSAR[b]	N/A
Kujath *et al.*, 1993	PSAR[c]	PSAR[c]	N/A	N/A	N/A	PSAR[c]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[c]	N/A	N/A
Zheng *et al.*, 2017	PSAR[d]	PSAR[d]	N/A	N/A	N/A	N/A	N/A	NSAR[d]	N/A	N/A	N/A	N/A	N/A	NSAR[d]	N/A
Ho and Omari, 2017	PSAR[e]	NSAR[e]	N/A	N/A	NSAR[e]	N/A	NSAR[e]	N/A	N/A	NSAR[e]	N/A	N/A	N/A	NSAR[e]	NSAR[e]
Manafi Rasi *et al.*, 2012	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
USING AN ENDPOINT OF SYMPTOMATIC VTE, DETECTED BY CLINICAL FOLLOW UP AND TARGETED INVESTIGATION															
Riou *et al.*, 2007	PSAR[f]	NSAR[f]	N/A	N/A	NSAR[f]	NSAR[f]	NSAR[f]	NSAR[f]	N/A	NSAR[f]	N/A	N/A	PSAR[f]	PSAR[f]	PSAR[f]
Hanslow *et al.*, 2006	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[g]	PSAR[g]	N/A	N/A	N/A	N/A	N/A	PSAR[g]	PSAR[g]
Jameson *et al.*, 2014	NSAR[h]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[h]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Makhdom *et al.*, 2013	PSAR[i]	NSAR[i]	N/A	N/A	NSAR[i]	N/A	N/A	NSAR[i]	N/A	NSAR[i]	N/A	N/A	N/A	N/A	N/A
Meek and Tong,	PSAR[j]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[j]	NSAR[j]	N/A

2012															
Patel *et al.,* 2012	PSAR[k]	NSAR[k]	N/A	N/A	N/A	N/A	NSAR[k]	NSAR[k]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wahlsten *et al.,* 2015	PSAR[L]	PSAR[L]	PSAR[L]	N/A	NSAR[L]	N/A	PSAR[L]	N/A	N/A	PSAR[L]	N/A	N/A	N/A	N/A	N/A
van Adrichem *et al.,* 2014	PSAR[m]	PSAR[m]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[m]	PSAR[m]	N/A	N/A	PSAR[m]	N/A	N/A

PSAR, Positive significant association reported; NSAR No significant association reported; N/A No attempt to report or analyse in the published manuscript; BMI, body mass index; CI, confidence interval; LMWH, low molecular weight heparin; VTE, venous thromboembolism; OR, Odds Ratio.

[a] Multivariate logistic regression - p=0.001 for age, p=0.009 for injury type, otherwise reported as showing no association for the relevant prespecified variables.
[b] Descriptive statistics – comparison of percentages only, with Fishers exact testing. Associated risk factors highlighted in discussion section. Notable that no patients in the LMWH group had a VTE event.
[c] Descriptive statistics – comparison of percentages only. Associated risk factors highlighted in table 2, 3 and discussion section.
[d] Binary logistic regression analysis, noting odds ratio of 1.050 (95% CI: 1.014 to 1.088, p=0.007) for advancing age, and of 1.201 (95% CI: 1.034 to 1.395, p=0.016) for high BMI, with no evidence of association between comorbidity, immobilisation type or gender and outcome of VTE detected.
[e] Direct comparison of percentages using Fisher exact, or continuous variables using independent T test. P=0.011 for age, other identified risk factors all failing to reach predefined significance level. Notable that analysed group only N=35.
[f] Logistic regression technique described, suggesting the following associations: odds ratio of 3.14 (2.27 to 4.33) for age>50, 2.70 (1.66 to 4.38) for rigid immobilisation, 4.11 (1.72 to 9.86) for non-weight-bearing and 1.88 (1.34 to 2.62) for severe injury
[g] Descriptive statistics, with p values presented for direct comparisons without mention of statistical test. Significant comorbidity, prior VTE and weightbearing status were noted to be associated with VTE development (p=0.04, 0.02 and 0.003 respectively.). Logistic regression also performed, highlighting plaster immobilisation as an independent predictor of risk (no odds ratio presented).
[h] Logistic regression analysis using univariate and multivariable analysis. Odds ratio of 11.97 (95% CI: 5.14 to 27.87, p<0.001) reported for a Charlson score of ≥1. No significant association of age with subsequent PE on univariate or multivariate analysis.
[i] Fishers exact test used to compare categorical variable. Higher proportional rate of VTE for patients >40 years (p=0.0026). No significant association seen regarding VTE and categorised BMI, co-morbidity and exogenous oestrogen use.
[J] Multivariable logistic regression - Odds ratio of 3.48 (1.11 to 10.89) for age, and 0.16 (0.03 to 0.80) for soft tissue injury compared to Achilles repair. No association seen between VTE development and gender, immobilisation type and length of stay.
[k] Categorical variables assessed using fishers exact test; Age >40 deemed to be associated with higher risk (p=0.016). No association with BMI, comorbidity or prior VTE and no presentation of significant odds ratios on further multivariable analysis.
[L] Multivariable cox regression - Hazard ratios of 1.13 for age, 4.15 for exogenous oestrogens, 6.27 (4.18 to 9.40) for prior VTE, 1.65 (1.12 to 2.42) for active cancer and 2.68 (1.66 to 4.33) for increased BMI.
[M] Adjusted odds ratios reported following binary logistic regression; OR of 12.7 (6.6 to 24.6) for traumatic indication (versus non-traumatic), 18.2 (6.2 to 53.4) for oral contraceptive use, 17.2 (5.4 to 55.2) for obesity and 23.0 (11.5 to 44.6) for known thrombophilia

Table 4: Other identified individual risk factors and their association with developing VTE

Study	Other risk factors shown to be associated with VTE	Risk factors shown to have no association with VTE	Other key findings / authors conclusions
Gehling *et al.,* 1998	• NR	• Unable to demonstrate association between cumulative risk factors and thrombosis	Non relevant
Goel *et al.,* 2009	• NR	• Gender • Comorbidities • BMI	Given the overall number of fractures, it is difficult to define a specific type as increasing the risk for DVT, but those of the tibial plateau did display a tendency towards higher rates of DVT in the study
Kock *et al.,* 1995	• NR	• Gender • Exogenous oestrogen • BMI	Treatment procedures involving less immobilisation should be used whenever possible.
Kujath *et al.,* 1993	• NR	• Smoking • Prior VTE • Exogenous oestrogen	The patients who did not develop a thrombosis had an average of 1.24 risk factors, whereas the patients with thrombosis had an average of 1.96 risk factors. The patients who suffered a thrombosis despite prophylaxis had 2.7 risk factors.
Zheng *et al.,* 2017	• NR	• NR	The study was not statistically powered to properly cull out any additional potential risk factors that might affect VTE incidence in this population
Riou *et al.,* 2007	• Non weight bearing status (OR 4.11, 95% CI: 1.72 to 9.86)	• No association seen on multivariate regression with: ○ VTE development and cancer ○ Exogenous oestrogen and comorbidity	Due to a very low incidence of certain variables (cancer, severe diseases and hormonal treatment), the power of the study was not sufficient to identify their roles as potential risk factors. Because the incidence of obesity was not high in study population, the results may not apply to morbidly obese patients
Hanslow *et al.,* 2006	• Air travel (multivariate logistic regression) • History of rheumatoid arthritis (multivariate logistic regression)	• Tourniquet use and mode of anaesthesia for those undergoing operative intervention	The incidence of thromboembolic disease after foot and ankle surgery could be higher than that previously reported particularly if a patient has certain risk factors
Jameson *et al.,* 2014	• Charlson score of ≥1 gives an OR of 11.97 (95% CI: 5.14 to 27.87,	• Age • Gender	Comorbidities elevate the risk of PE and these data can be utilised by clinicians when considering whether to prescribe

	p<0.001)		LMWH for VTE prophylaxis with the attendant risks of the therapy itself borne in mind.
Makhdom *et al.,* 2013	• NR	• Smoking • BMI • Exogenous oestrogen use • Steroid use	Patient education is necessary regarding anticipated complications, and early mobilisation should be advocated, especially for patients older than 40 years of age.
Meek and Tong, 2012	• Achilles tendon rupture (descriptive)	• Gender, • Soft tissue injury • Method of immobilisation • Emergency department length of stay • Surgical intervention.	Increasing age and a diagnosis of Achilles tendon rupture appeared to increase the risk of VTE.
Patel *et al.,* 2012	• NR	• Age, comorbidity, Previous VTE, BMI, operative intervention	Congestive heart failure, history of DVT or PE, and obesity might be risk factors, but perhaps the study did not have an adequate number of patients to show this difference.
Wahlsten *et al.,* 2015	• Coagulopathy (HR 2.47, 95% CI: 1.1 to 5.7) • Peripheral arterial disease (HR 2.34, 95% CI: 1.2 to 4.6) • nonsteroidal anti-inflammatory drugs use (HR 1.3, 95% CI: 1.1 to 1.6)	• Smoking. • Statin therapy and use of ACE inhibitor medications appeared to convey a protective effect, with HR 0.8 and 0.6 respectively.	Patients with risk factors, especially previous DVT or PE, use of oral contraceptives, and extreme obesity, have an increased risk of DVT/PE that exceeds the risk of DVT/PE in healthy patients undergoing total hip or knee replacement
van Adrichem *et al.,* 2014	• The presence of 2 or more acquired or genetic risk factors in patients with below knee cast immobilisation produced an OR of 43.4 (95% CI: 13.4 to 141.0)	• Gender	Patients with below-knee cast immobilisation have a substantially increased risk of venous thrombosis, i.e. a 56-fold increased risk as compared with patients with no cast, corresponding to an estimated incidence of 1% in the first 3 months after cast application
Ho and Omari, 2017	• Subsequent presentation with symptoms suggestive of DVT (p=0.006)	• Gender • BMI • Type of injury • Type of immobilisation • Weight bearing status • Smoking • Exogenous oestrogen use	This pilot study unveiled limitations and logistical issues to be addressed in the future. Notably, the limitations include the small number of patients and the low adherence to attending ultrasound assessment.

		• Family history of VTE	
Manafi Rasi *et al.,* 2012	• Cumulative number of risk factors - presence of 3 or more risk factors reported as significantly associated with VTE development (p=0.01)	NR	The incidence of DVT significantly increased in the presence of 3 or more risk factors (p=0.01)

ACE, angiotensin-converting-enzyme; BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low molecular weight heparin; NR, Not reported or analysed; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism

Figure 1: **Flow chart of abstract screening, exclusion and final selection**

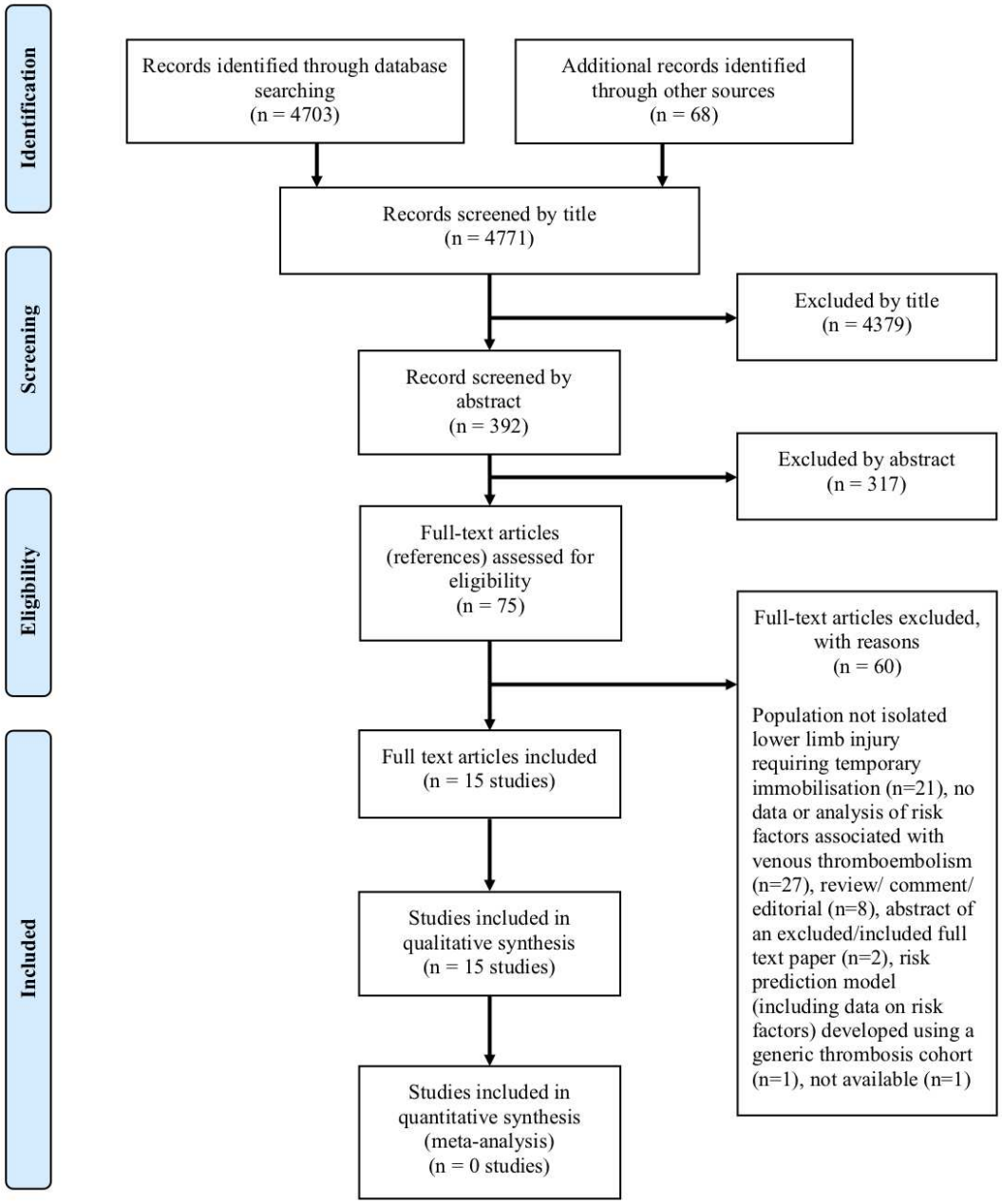

Figure 2: **ROBINS-I risk of bias assessment graph: Review authors' judgements about each methodological quality item across all included studies - Review of individual risk factors associated with VTE risk**