Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilization 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 1.5–3.48).
• We found limited evidence to support the use of other risk factors within prediction models.

Summary. Background: Patients immobilized 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 immobilization. Methods: Several electronic databases were searched from inception to May 2017. Any studies that included a measurement of VTE as a patient outcome in adults requiring temporary immobilization (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 synthesize 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.

Keywords: casts; immobilization; risk; surgical; venous thromboembolism.
balance of benefit and risk from thromboprophylaxis remains unclear.

Outpatients placed in temporary lower limb immobilization 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 immobilization (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 that also suggest that in cohorts without overt additional risk factors, the incidence of clinically relevant VTE in immobilized 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 immobilization, 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 dichotomized without evidential support. In addition, it is unclear whether these scores are designed to detect all VTEs; 80% of deep vein thromboses (DVTs) can be clinically silent initially, a statistic that perhaps explains embolization accounting for 30% of first VTE presentations [20]. The validity of scoring systems and risk factors therefore varies 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 immobilization. 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 immobilization, 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 10 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 immobilization) with risk factor assessment or risk prediction modelling terms (used in the searches of MEDLINE, the 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 (A.P.) 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 (A.P. and D.H.). Any disagreements in the selection process were resolved through discussion with a third reviewer (S.G.) and included by consensus.

Studies were considered eligible for inclusion if they met the following criteria: (i) any study design that included a measurement of VTE patient outcome (symptomatic and/or asymptomatic); (ii) adults (age over 16 years) requiring temporary immobilization (e.g. leg cast or brace in an ambulatory setting) for an isolated lower limb injury; and (iii) any studies that reported and analyzed 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 (A.P.) into a
standardized data extraction form and independently checked for accuracy by a second reviewer (D.H.). Any discrepancies were resolved through discussion to achieve agreement. Where differences were unresolved, a third reviewer’s opinion was sought (S.G.).

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, ACRÒBAT-NRSI) [22]. The tool is based on the original Cochrane risk of bias tool for randomized 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 analyzed using this tool [22] regardless of whether the original study design included randomization 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 sequela 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 as a result of significant levels of heterogeneity between studies, variable reporting items and the high risk of attributable bias. Descriptive statistics and thematic analysis were used to synthesize 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 summarizes 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 summarized 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 10 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], and 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 immobilization. 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 43.8% [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 3 months [28–31,34,37–41] and one study followed-up patients for 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] and six studies collected these 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 immobilization 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].
| 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 immobilization with plaster or bandages (and at least one risk factor for VTE) | n = 287, 50.5% male, mean age 36.3* | 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 18-75 years with unilateral displaced fractures below the knee requiring operative intervention | n = 238, 62% male, mean age 40.5* | LMWH group: 8.7% Control group: 12.6% | No prophylaxis prior to randomization | 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 18-65 years undergoing conservative treatment for below knee injury with cylinder or below knee cast | n = 339, 61% male, mean age 33.8* | LMWH group: 0% Control group: 4.3% | No prophylaxis prior to randomization | NR (however, duration of cast: 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 > 7 days | n = 253, 58% male, mean age 34.3* | LMWH group: 4.8% Control group: 16.5% | No prophylaxis prior to randomization | NR (however, duration of cast: LMWH group, 15.6 days; control group, 15.8 days) | Physician assessment (prospective) | Compression ultrasound by two examiners and confirmation phlebography | NR (appears descriptive) |
### Table 1 (Continued)

| 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 |
|-----------------------|-----------------|---------------------------|-----------------------------|------------------|-------------|-----------------------|-------------------------|---------------------|---------------------|
| 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 | 814, 62.3% male, mean age 47.8 | LMWH group: 1.5% Control group: 3.2% | No prophylaxis prior to randomization | 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 (immobilization duration > 7 days) | 2761, 51% male, mean age 40 | 6.4% | Antithrombotic prophylaxis was given to 61% of 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 | 602, 52% male, mean age 42.9 | 5.3% | Antithrombotic prophylaxis was given to 31% of 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 | 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 Setting: outpatient until surgery, short day-case stay thereafter | All patients undergoing Achilles tendon repair | 115, 86.1% male, mean age 41 | 23.5% | No peri- or postoperative prophylaxis | 3 months | Collected from electronic medical record system (retrospective) | Case note search, including hospital re-attendance and diagnostic imaging | Non-parametric testing using Fisher’s exact test |
| 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 |
|-----------------------|----------------|--------------------------|---------------------------|------------------|-------------|----------------------|-------------------------|----------------------|---------------------|
| Meek & Tong, 2012, Australia | Design: retrospective cohort study Setting: outpatient | Age > 18 years with acute lower limb injury requiring temporary immobilization (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 | $n = 1172$, sex 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 | $n = 57619$, 51.4% male, mean age 52.6* | 1.0% | Routine perioperative prophylaxis with nil postoperative | 180 days | Collected from five 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: mostly outpatient, some with short inpatient stays (< 3 days) | Age 18–70 years with a first VTE identified at an anticoagulation clinic (cases) Control group identified by random dialing method (matched for sex and age) | $n = 10567$,† sex NR, mean age NR | NR | No data recorded | 3 months | Participant completed questionnaire (prospective collection) | Case note search, including hospital re-attendance and diagnostic imaging | Logistic regression |
| Ho & 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 |
The overall methodological quality of the 15 included studies is summarized in Fig. 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 as at serious risk of bias did so predominately on selection of participants into the study, perhaps highlighting the issue with retrospective observational work on 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 11 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 [28,30,32,34,37,38].

Both age and BMI feature in the published and most widely used risk prediction models. Injury type and severity are 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 immobilization 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 eight out of ten studies and six out of seven studies, respectively. The effects of these exclusions on other risk factor variables are presented in Tables S3 and S4.

We found a few other individual risk factors in this study not included in current scoring systems, but
Bias due to confounding
Bias in selection of participants for study
Bias in 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

Fig. 2. ROBINS-I risk of bias assessment graph.

Table 2 ROBINS-I risk of bias assessment summary: review authors’ judgements about each methodological quality item for each included study.

| Study                      | Bias due to confounding | Bias in selection of participants into the study | Bias in classification/ measurement of interventions | Bias because of deviations from intended interventions | Bias because of missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall* |
|----------------------------|-------------------------|-------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-----------------------------|------------------------------------|------------------------------------------|----------|
| 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                                               | Moderate                    | Moderate                           | Moderate                                  | Moderate |
| Kujath et al., 1993        | Low                     | Low                                             | Moderate                                              | Moderate                                               | Moderate                    | Moderate                           | Moderate                                  | Moderate |
| Zheng et al., 2017         | Moderate                | Moderate                                        | Moderate                                              | Serious                                                | Moderate                    | Moderate                           | Moderate                                  | Serious  |
| 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 & 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 & Omari, 2017           | Serious                 | Serious                                         | Moderate                                              | Serious                                                | Moderate                    | Moderate                           | Moderate                                  | Serious  |
| Manafi Rasi et al., 2012   | Serious                 | Moderate                                        | Moderate                                              | Moderate                                               | Moderate                    | Moderate                           | Moderate                                  | Serious  |

*Overall risk of bias judgement (equal to the most severe level of bias found in any domain) was judged as: (i) low risk of bias, study comparable to a well-performed randomized trial; (ii) moderate risk of bias, sound for a non-randomized study but not comparable to a rigorous randomized trial; (iii) serious risk of bias, the study has some important problems; (iv) critical risk of bias, too problematic to provide any useful evidence on the effects of intervention.

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

| Study | Using an endpoint of asymptomatic VTE, detected by routine screening | Permanent (present before episode of lower limb immobilization) | Using an endpoint of symptomatic VTE, detected by clinical follow-up and targeted investigation | Transient (during injured period) |
|-------|------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------|
| Gehling et al., 1998 | N/AS ARa N/A N/A | N/A N/A | N/A N/A | N/A N/A |
| Goel et al., 2009 | PSARa NSARa N/SARa | N/A N/A | NSARa NSARa | N/A N/A |
| Kock et al., 1995 | PSARb NSARb N/A | N/A N/A | NSARb NSARb | N/A N/A |
| Kujath et al., 1993 | PSARc PSARc N/A | N/A N/A | PSARc PSARc | N/A N/A |
| Zheng et al., 2017 | PSARd PSARd N/A | N/A N/A | PSARd PSARd | N/A N/A |
| Ho & Oman, 2017 | PSARe NSARe N/A | N/A N/A | NSARe NSARe | N/A N/A |
| Manafi Rasi et al., 2012 | 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 | PSARf NSARf N/A | N/A N/A | PSARf PSARf | PSARf |
| Hanskov et al., 2006 | N/A N/A | N/A N/A | PSARg PSARg | N/A N/A |
| Jameson et al., 2014 | N/A N/A | N/A N/A | N/A N/A | N/A N/A |
| Makhdom et al., 2013 | PSARi NSARi N/A | N/A N/A | PSARi NSARi | N/A N/A |
| Meek & Tong, 2012 | PSARj N/A | N/A N/A | N/A N/A | N/A N/A |
| Patel et al., 2014 | PSARk NSARk N/A | N/A N/A | PSARk NSARk | N/A N/A |
| Wahlsten et al., 2014 | PSARl PSARl N/A | N/A N/A | PSARl PSARl | N/A N/A |
| van Adrichem et al., 2014 | PSARM PSARM N/A | N/A N/A | PSARM PSARM | N/A N/A |

PSAR, positive significant association reported; NSAR, no significant association reported; N/A, no attempt to report or analyze in the published manuscript; BMI, body mass index; CI, confidence interval; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism; OR, odds ratio. aMultivariate logistic regression: P = 0.001 for age, P = 0.009 for injury type, otherwise reported as showing no association for the relevant prespecified variables. bDescriptive statistics; comparison of percentages only, with Fisher’s exact test. Associated risk factors highlighted in discussion section. It is notable that no patients in the LMWH group had a VTE event. cDescriptive statistics; comparison of percentages only. Associated risk factors highlighted in Tables 23 and discussion section. dBinary logistic regression analysis, noting odds ratio of 1.050 (95% CI, 1.014–1.088; P = 0.007) for advancing age, and of 1.201 (95% CI, 1.034–1.395; P = 0.016) for high BMI, with no evidence of association between comorbidity, immobilization type or gender and outcome of VTE detected. eDirect comparison of percentages using Fisher’s exact test, or continuous variables using independent t-test. f0.011 for age; other identified risk factors all failing to reach predefined significance level. It is notable that the analyzed group is only n = 35. gLogistic regression technique described, suggesting the following associations: odds ratio of 3.14 (2.27–4.33) for age > 50 years, 2.70 (1.66–4.38) for rigid immobilization, 4.11 (1.72–9.86) for non-weight-bearing and 1.88 (1.34–2.62) for severe injury. hDescriptive statistics, with P values presented for direct comparisons without mention of statistical test. Significant comorbidity, prior VTE and weight-bearing status were noted to be associated with VTE development (P = 0.04, 0.02 and 0.003, respectively). Logistic regression also performed, highlighting plaster immobilization as an independent predictor of risk (no odds ratio presented). iLogistic regression analysis using univariate and multivariable analysis. Odds ratio of 11.97 (95% CI, 5.14–27.86; P < 0.001) reported for a Charlson score of ≥ 1. jNo significant association of age with subsequent PE on univariate or multivariate analysis. kPSAR, positive significant association reported; N/SAR, no significant association reported; N/A, no attempt to report or analyze in the published manuscript. lLogistic regression analysis using univariate and multivariable analysis. Odds ratio of 18.2 (6.2–53.4) for oral contraceptive use, 17.2 (5.4–55.2) for obesity and 23.0 (11.5–44.6) for known thrombophilia. mAdjusted odds ratios reported following binary logistic regression; OR of 1.27 (6.6–24.6) for traumatic indication (vs. non-traumatic).
associated with subsequent development of VTE after lower limb immobilization. These included recent air travel (one study) [29] and 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].

The 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 estrogen use and VTE [28,30,32,34], and six studies reported no association between smoking and subsequent VTE [28,30,32,34,38,40]. Several papers produced conflicting results; six studies reported no association between raised BMI and subsequent risk of VTE [28,30,32,34,37,38] 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 immobilization 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 immobilization 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 [42]. Our study was conducted with robust methodology and was undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination [43]. 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 randomized 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 [44]. 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 immobilized for a period of 4-8 weeks in total. Debate also persists about the type and duration of thromboprophylaxis in this setting. Outside randomized 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/immobilized limb. Although 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 generalized prothrombotic state and that modification of treatment plans/immobilization strategies could be more beneficial than generic prophylaxis.

All the studies within our review were classified as at moderate or severe risk of bias. As such, any conclusions regarding the influence of risk factors on the subsequent development of VTE 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.

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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 estrogen • BMI                 | Treatment procedures involving less immobilisation should be used whenever possible. 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. |
| Kujath et al., 1993    | • NR                                               | • Smoking • Prior VTE • Exogenous estrogen          | The study was not statistically powered to properly cull out any additional potential risk factors that might affect VTE incidence in this population 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 |
| Zheng et al., 2017     | • NR                                               | • NR                                               | 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 Comorbidities elevate the risk of PE and these data can be utilised by clinicians when considering whether to prescribe LMWH for VTE prophylaxis with the attendant risks of the therapy itself borne in mind. Patient education is necessary regarding anticipated complications, and early mobilisation should be advocated, especially for patients older than 40 years of age. Increasing age and a diagnosis of Achilles tendon rupture appeared to increase the risk of VTE. 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. |
| Riou et al., 2007      | • Non-weight-bearing status (OR, 4.11; 95% CI, 1.72–9.86) | • No association seen on multivariate regression with: ○ VTE development and cancer ○ Exogenous estrogen and comorbidity | |
| Hanslow et al., 2006   | • Air travel (multivariate logistic regression) • History of rheumatoid arthritis (multivariate logistic regression) | • Tourniquet use and mode of anesthesia for those undergoing operative intervention | |
| Jameson et al., 2014   | • Charlson score of ≥ 1 gives an OR of 11.97 (95% CI, 5.14–27.87; P < 0.001) | • Age • Gender | |
| Makhdom et al., 2013   | • NR                                               | • Smoking • BMI • Exogenous estrogen use • Gender • Soft tissue injury • Method of immobilisation • Emergency department length of stay • Surgical intervention. | |
| Meck & Tong, 2012      | • Achilles tendon rupture (descriptive)            | • Age, comorbidity, previous VTE, BMI, operative intervention | |
| Patel et al., 2012     | • NR                                               | • | 
Table 4 (Continued)

| Study                          | Other risk factors shown to be associated with VTE                                                                 | Risk factors shown to have no association with VTE                                                                 | Other key findings/authors conclusions                                                                 |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Wahlsten et al., 2015         | - Coagulopathy (HR, 2.47; 95% CI, 1.1–5.7)                                                                     | - Smoking                                                                                                            | 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 |
|                               | - Peripheral arterial disease (HR, 2.34; 95% CI, 1.2–4.6)                                                        | - Statin therapy and use of ACE inhibitor medications appeared to convey a protective effect, with HR 0.8 and 0.6, respectively. |                                                                                                        |
|                               | - Non-steroidal anti-inflammatory drugs use (HR, 1.3; 95% CI, 1.1–1.6)                                          |                                                                                                                     |                                                                                                        |
| van Adrichem et al., 2014     | - The presence of two or more acquired or genetic risk factors in patients with below knee cast immobilization produced an OR of 43.4 (95% CI, 13.4–141.0) | - Gender                                                                                                            | Patients with below-knee cast immobilization 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 & Omari, 2017               | - Subsequent presentation with symptoms suggestive of DVT (P = 0.006)                                             | - Gender                                                                                                            | 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. |
| Manafi Rasi et al., 2012       | - Cumulative number of risk factors: presence of three or more risk factors reported as significantly associated with VTE development (P = 0.01) | - Type of injury                                                                                                     | 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 analyzed; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

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 immobilization, discharged to an outpatient setting. Previous work has attempted to address a similar issue in patients undergoing elective foot and ankle surgery [45–47]. We consider this to be a different population because of the pathological differences between blunt force and surgical trauma, expert image-guided reduction and postoperative immobilization regimes.

Advancing age has long been recognized as an established risk factor for VTE [48]. 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 as a result of variable methodology. Indeed, our demonstration of advancing age as a consistent individual risk factor for VTE probably reflects the increasing prothrombotic state seen with aging, irrespective of immobilization. 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 [49,50].

The hypothesis that extent of injury acts as a predictor of VTE risk is in keeping with those studies that report a low VTE incidence in patients with immobilization following soft tissue injury [38]. In addition, there is face validity of 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 immobilization; patients with severe fracture patterns are more likely to be placed in stricter and more extensive immobilization. Lastly, we found only two studies identifying cumulative risk with an increased incidence of VTE [35,39]. Although this is perhaps intuitive, the supporting data appear 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 an 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 an attempt to derive a full, restricted and clinical decision rule for use in this population. Age and BMI featured in all three models, with odds ratios reported on univariate analysis of 3.2 (95% CI, 2.9–3.6) for age ≥ 55 and 3.1 (95% CI, 2.5–3.9) for BMI ≥ 35. No specific candidate variable in this study referred to injury type. However, the extent of immobilization was specifically assessed as a predictor, with odds ratios of 10.7 (95% CI, 4.3–26.6) and 8.7 (95% CI, 5.5–13.7) for complete leg and lower leg casts, respectively, when compared to no cast immobilization. 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, 3.3–41.2). We found no evidence from other studies that would support this grade of association.

The findings from this systematic review suggest that although common generic predictors of risk of 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 with exogenous estrogens. However, such research will have challenges in a health system with national guidance prompting consideration of risk and bespoke prescribing [7,44]. In addition, the low frequency of events may result in real difficulty obtaining valid data sets. Such studies would need careful assessment of baseline risk, transparent reporting of thromboprophylaxis and an independently adjudicated, patient-centered 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 immobilization after acute injury. All studies included in the review were deemed to be 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.

Addendum
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.

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Disclosure of Conflict of Interests
On behalf of all authors, I declare no known conflict of interests to exist regarding this research article.

Supporting Information
Additional Supporting Information may be found in the online version of this article:
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).

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