Thromboprophylaxis in lower limb immobilisation after injury (TiLLI)

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ABSTRACT
Venous thromboembolic disease is a major global cause of morbidity and mortality. An estimated 10 million episodes are diagnosed yearly; over half of these episodes are provoked by hospital admission/procedures and result in significant loss of disability adjusted life years. Temporary lower limb immobilisation after injury is a significant contributor to the overall burden of venous thromboembolism (VTE). Existing evidence suggests that pharmacological prophylaxis could reduce overall VTE event rates in these patients, but the proportional reduction of symptomatic events remains unclear. Recent studies have used different pharmacological agents, dosing regimens and outcome measures. Consequently, there is wide variation in thromboprophylaxis strategies, and international guidelines continue to offer conflicting advice for clinicians. In this review, we provide a summary of recent evidence assessing both the clinical and cost effectiveness of thromboprophylaxis in patients with temporary immobilisation after injury. We also examine the evidence supporting stratified thromboprophylaxis and the validity of widely used risk assessment methods.

CASE 1
A 60-year-old woman attends your department after a fall downstairs, injuring her right ankle. X-rays confirm a Weber B fracture to the lateral malleolus without talar shift. There is no pain to the medial aspect. The orthopaedic plan is for below-knee plaster immobilisation in a non-weight-bearing cast, conservative management and outpatient review in 7–10 days’ time. On further assessment, a body mass index (BMI) of 35 is apparent, along with a history of chronic obstructive pulmonary disease.

CASE 2
A 25-year-old man attends your department after a crush injury to his left foot sustained at work. X-rays reveal undisplaced fourth and fifth metatarsal neck fractures. The orthopaedic team advise a walking boot and to allow partial weight bearing as tolerated until outpatient review later that week. On further assessment, the patient has no other medical history and no family history of venous thromboembolism (VTE). He takes no medications. Despite analgesia in the department, he remains unable to put any weight through the affected limb.

QUESTION
Should these patients be offered thromboprophylaxis to reduce their short-term risk of VTE?

To answer that question, we will provide a short summary of the problem, followed by a review of the evidence and a practical guide to decision-making and intervention in these clinical scenarios.

BACKGROUND
VTE is a significant global health burden, with incident events alone costing the UK an estimated £640 million and the USA an estimated $7–10 billion each year.1,2 Within the last decade, VTE has resulted in more deaths than prostate cancer, breast cancer, road traffic accidents and AIDS combined.3

Temporary immobilisation after injury accounts for approximately 2% of all VTE cases in registry data.4 These cases are potentially preventable with early pharmacological thromboprophylaxis. However, it is unclear which patients will benefit from such intervention, which will be harmed, whether clinical outcomes are improved as a result of treatment and whether prophylaxis is cost-effective. As a result, international guidelines continue to recommend different management options; the UK advises routine assessment and individualised prescribing, for example, whereas US guidelines advise against thromboprophylaxis in this population.5-6

This issue was recently highlighted as a research priority for emergency medicine, through the James Lind Alliance Priority Setting Partnership in the UK.7 While the debate continues, case report data and media coverage continue to highlight recurrent and tragic outcomes.8,9 It remains unclear whether these tragedies were avoidable. In many regions, legal rulings and recommendations by the coroner/medical examiner delivered with the aim of avoiding future deaths have forced the clinical agenda without recourse to scientific evidence.10 Practice remains variable with differing levels of engagement and awareness, despite the relative frequency of the problem. It is imperative that a cross-specialty consensus is reached on management of VTE risk, to ensure that clinicians and patients can be adequately informed and counselled on the merits of intervention.

This article summarises recent work on this topic and provides pragmatic guidance and decision support for clinicians.

What is the risk of VTE following lower limb injury and temporary immobilisation?

A recent Cochrane review on this topic suggests wide variation in the incidence of VTE following lower
limb immobilisation without thromboprophylaxis, reporting a range between 4.3% and 40.0% within the literature. These figures are based on the outcome of ‘any VTE’, including routine screening and detection of isolated distal deep vein thrombosis (DVT). There is ongoing debate regarding the clinical relevance of such a composite endpoint and the sensitivity of the contributing diagnostics. Of more importance to clinicians and patients is the incidence of morbidity after immobilisation. This is more challenging to define but suggested by many to be the incidence of only clinically relevant or symptomatic VTE, warranting repeat hospital attendance and/or intervention. Accurate estimates of this endpoint suffer from limitations in the injured population regarding subjectivity. When should a clinician or patient suspect VTE in a leg that is painful and swollen at baseline from injury? However, recent studies with transparent reporting of clinically relevant outcomes demonstrate a high level of consistency. The recent Cochrane review extracted data from six studies involving just under 3000 randomised patients; symptomatic VTE occurred in 1.8%–5.5% of conservatively managed patients. These results suggest that without thromboprophylaxis, approximately 1 in every 50 patients will suffer a symptomatic VTE event (including symptomatic distal and proximal DVT and pulmonary embolism (PE)) following temporary immobilisation after injury. This is likely to be an underestimate given the range previously mentioned, the exclusion of high-risk patients from trial design and the general health equity of patients willing to engage with research.

**Is thromboprophylaxis clinically effective?**

Can pharmacological thromboprophylaxis reduce this morbidity burden and, if so, by what margin? We performed a recently updated systematic review and network meta-analysis to compare any pharmacological intervention against control for this defined population. This review included the Prevention of Thrombosis after Lower Leg Plaster Cast (POT-CAST) trial, which has reignited debate on this important topic, and other recent randomised studies assessing the novel use of fondaparinux for this indication. We identified 13 trials with 68.57 patients suitable for inclusion. Interventions included prophylactic dose low molecular weight heparin (LMWH) or fondaparinux only. We examined four additional trials that had been excluded from the previous Cochrane review and one trial published subsequently. We found no trial evidence examining the use of direct oral anticoagulants (DOACs) in this situation. Risk of bias was present in all included studies. We found that both LMWH and fondaparinux significantly reduced the odds of clinically detected DVT, PE and any VTE. Intervention appeared to halve the risk of VTE across all classifications. It follows that the absolute 2% risk of clinically significant VTE following temporary immobilisation after injury can be effectively halved to 1% with prophylactic dose anticoagulation. Although this may represent a potentially high number needed to treat, this value would depend primarily on baseline risk (which is likely to vary within the population) and also would be considered in the context of prevalence. Approximately 70,000 patients are immobilised and discharged from EDs in the UK alone every year. Even a 1% absolute risk reduction in the VTE event rate in this cohort would therefore represent prevention of 700 clinically relevant VTE events. Assuming these events would be detected and treated as provoked VTE in the absence of thromboprophylaxis, they would incur 63,000 patient days of therapeutic dose anticoagulation, with accompanying costs and harms.

**What are the harms of thromboprophylaxis?**

Clear definitions are now in place for the identification and classification of bleeding events in trials of anticoagulation and thromboprophylaxis. Using these, our above systematic review found limited evidence of harm from prophylactic dose anticoagulation in this population. Only four major bleeding events were identified in total, with insufficient evidence of an increase within the LMWH group (OR 1.45, 95% CI 0.80 to 32.17). Although these results are inconclusive given the low frequency of events, only four events within a trial sample of just under 7000 patients provide some reassurance on safety. Minor bleeding as a secondary outcome varied across the population, being found in 0%–10.5% of patients treated with LMWH, in 0%–1.5% of patients treated with fondaparinux and in 0%–6.8% of the control groups. No cases of death attributable to VTE or intervention were identified within the study, and in those trials monitoring for the incidence of heparin-induced thrombocytopenia (HIT), no cases were detected. The most common adverse event of infection appeared equal between control and intervention groups when strictly defined.

**Do the benefits of thromboprophylaxis justify the risks?**

Thromboprophylaxis reduces the risk of thromboembolism but may increase the risk of bleeding. Our data were inconclusive on this latter aspect, but it remains one of the primary clinical concerns regarding the use of thromboprophylaxis. We undertook decision-analytic modelling to determine how these risks might compare in people undergoing lower limb immobilisation due to injury. Table 1 summarises the results. The risk of fatal PE (which often drives decisions and recommendations regarding thromboprophylaxis) is very small, and the reduction in this risk associated with thromboprophylaxis is roughly matched by an increase in the risk of fatal bleeding or non-fatal intracranial haemorrhage. Overall, the risk of death or non-fatal intracranial haemorrhage is about 1 in 4000, whether thromboprophylaxis is

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Predicted clinical outcomes per 100 000 patients with lower limb immobilisation due to injury</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Outcomes at 6 months per 100 000 patients</td>
</tr>
<tr>
<td></td>
<td>Fatal PE</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>12</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>7</td>
</tr>
</tbody>
</table>

*Patients having other major bleeds could also have a DVT or non-fatal PE.

CTEPEH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

given or not. These are tragic events and, given the large population undergoing immobilisation, will occur with some frequency. However, our analysis suggests that thromboprophylaxis will not markedly change their incidence.

The main benefits of thromboprophylaxis lie in preventing non-fatal PE, symptomatic DVT and, in particular, asymptomatic DVT. Benefits for patients are assumed to accrue in the form of reduced long-term complications, particularly post-thrombotic syndrome. We estimated that, taking all effects into account, thromboprophylaxis results in 0.015 additional quality-adjusted life years (QALYs) per patient treated (95% credible interval (CrI 0.004 to 0.029)), indicating an overall benefit. However, it is uncertain whether a reduced risk of asymptomatic DVT leads to a reduced risk of post-thrombotic syndrome, so this finding should be treated with some caution.33

Is thromboprophylaxis cost-effective?
Given the cost implications of prophylaxis, the low absolute event rate and the potential implications of any recommendations it is necessary to examine the cost effectiveness of this intervention. Our recent work for the Health Technology Assessment Programme examined this in detail.23 We examined this intervention. Our recent work for the Health Technology Assessments it is necessary to examine the cost effectiveness of subsequent disease in this ambulatory cohort of patients. A further systematic review was conducted, identifying 15 studies and 80678 patients for inclusion. Meta-analysis of data was not possible due to significant variation between studies regarding data collection methods. All studies were deemed to be at moderate to severe risk of bias. We found advancing age and injury pattern to be consistently associated with increased VTE risk. BMI was the third most consistent individual risk highlighted, although overall results were conflicting. A total of 12 other risk factors analysed did not demonstrate any consistency in association with VTE across the dataset.33 A subsequent publication supports our findings, reporting injury pattern, family history and BMI to be the individual risk factors most associated with VTE risk, within the POT CAST trial cohort.40

We conducted a further systematic review and engaged topic experts to try and identify available RAMs for use in this population. This work identified seven RAMs, three of which have undergone attempted external validation.36 41–46 Variation and essential characteristics of the identified RAMs are presented in table 2. All studies looking to derive or externally validate a RAM were deemed to be at high risk of bias and did not report discrimination or calibration within an appropriate external population.

Prognostic accuracy measures for the three scores evaluated in two validation studies are presented in table 3. RAM sensitivity varies from 57.1% to 92.6% and specificity varies from 4.76% to 60.8%. As an ordinal score with additional validation data, the L-TRiP(cast) RAM is displayed in this table using thresholds denoting optimal performance and to allow direct comparison with other validated scores. The area under the receiver operating characteristic curve for the L-TRiP(cast) score ranged from 0.77 (95% CI 0.66 to 0.87) in the derivation cohort to 0.77 (95% CI 0.58 to 0.96) and 0.95 (95% CI 0.91 to 0.99) in the two subsequent validation cohorts. In addition, subsequent retrospective evaluation of the L-TRiP(cast) score within the POT CAST cohort reports a lower area under the curve value of 0.69 (95% CI 0.58, 0.80).40 As such, although the concept of a RAM is intuitive in this situation, the available supporting

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**Table 2** Summary of design characteristics and threshold levels of identified RAMs

<table>
<thead>
<tr>
<th>Risk assessment model</th>
<th>Acronym/descriptor</th>
<th>Derivation</th>
<th>Design</th>
<th>Incorporation of bleeding risk?</th>
<th>Number of variables</th>
<th>Threshold (suggested cut-point)</th>
<th>Attempted validation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al32</td>
<td>The GEMNet guideline</td>
<td>EC</td>
<td>Dichotomous</td>
<td>Yes</td>
<td>11</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Keenan et al32</td>
<td>The Plymouth Rule</td>
<td>EC</td>
<td>Ordinal</td>
<td>No</td>
<td>14</td>
<td>&gt;2</td>
<td>Yes</td>
</tr>
<tr>
<td>Nemeth et al41</td>
<td>The L-TRiP(cast) score</td>
<td>Regression</td>
<td>Ordinal</td>
<td>No</td>
<td>14</td>
<td>&gt;8</td>
<td>Yes</td>
</tr>
<tr>
<td>Saragas et al41</td>
<td>The modified Caprini score</td>
<td>EC</td>
<td>Ordinal</td>
<td>No</td>
<td>36</td>
<td>&gt;1</td>
<td>No</td>
</tr>
<tr>
<td>Eingartner et al45</td>
<td>N/A</td>
<td>EC</td>
<td>Ordinal</td>
<td>No</td>
<td>9</td>
<td>&gt;1</td>
<td>No</td>
</tr>
<tr>
<td>Haque et al46</td>
<td>N/A</td>
<td>EC</td>
<td>Ordinal</td>
<td>No</td>
<td>14</td>
<td>&gt;2</td>
<td>No</td>
</tr>
<tr>
<td>Giannakakis et al44</td>
<td>N/A</td>
<td>EC</td>
<td>Dichotomous</td>
<td>No</td>
<td>12</td>
<td>N/A</td>
<td>No</td>
</tr>
</tbody>
</table>

EC, Expert Consensus; GEMNet, Guidelines in Emergency Medicine Network; L-TRiP(cast), Leiden Thrombosis Risk in Plaster (cast); N/A, not applicable; RAM, risk assessment method.
evidence is weak. Further RAMs (such as the Trauma, Immobilisation and Patients’ Characteristics (TIP) score) continue to be published using Delphi consensus methodology and other derivation techniques, reporting improved performance metrics on internal validation. All proposed RAMs remain in need of robust external validation.

What are the key uncertainties and challenges moving forward?
Can I use a DOAC for this indication?
There is no trial evidence examining the use of DOAC medications in this clinical scenario. As such, there are no available data on the clinical or cost effectiveness of these drugs. Any such use would be off licence and approved as part of a trust protocol using local pharmacy and thrombosis committee governance structures.

Many trusts have taken this option and are starting to publish prospective datasets recording their experience. Evaluation of this strategy with organisational support and careful oversight is to be encouraged and will provide estimates of effectiveness and safety that may support the case for future research.

Does this evidence apply to temporary splints as well as plaster casts?
The majority of research in this area focusses on immobilisation in plaster. As such, all estimates of effectiveness are not necessarily generalisable to other forms of immobilisation, which may allow partial weight bearing or less restriction in mobility. However, a caution should be noted here; often patients are treated with advice to partially weight bear when they clearly cannot do so. These patients remain at risk of VTE through immobility. NICE advice to partially weight bear when they clearly cannot do so. A caution should be noted here; often patients are treated with partial weight bearing or less restriction in mobility. However, generalisable to other forms of immobilisation, which may allow casts?

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Diagnosis performance of the L-TRIP(cast), GEMNet and Plymouth risk assessment models

<table>
<thead>
<tr>
<th>Author</th>
<th>GEMNet</th>
<th>Plymouth</th>
<th>L-TRIP(cast) with a cut-point of 8 or above</th>
<th>L-TRIP(cast) with a cut-point of 9 or above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>85.7% (62.6% to 96.2%)</td>
<td>57.1%</td>
<td>92.6%</td>
<td>80.8%</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>4.76% (0.2% to 25.9%)</td>
<td>52.4%</td>
<td>39.7%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Positive predictive value (95% CI)</td>
<td>47.4% (31.3% to 64.0%)</td>
<td>54.5%</td>
<td>3.8%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Negative predictive value (95% CI)</td>
<td>25.0% (1.3% to 78.1%)</td>
<td>55.0%</td>
<td>99.5%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Likelihood ratio positive (95% CI)</td>
<td>0.90 (0.73 to 1.10)</td>
<td>1.20 (0.67 to 2.15)</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Likelihood ratio negative (95% CI)</td>
<td>3.00 (0.16 to 55.31)</td>
<td>0.81 (0.46 to 1.46)</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Proportion receiving thromboprophylaxis (95% CI)</td>
<td>90.5% (76.5% to 96.9%)</td>
<td>52.4% (36.6% to 67.7%)</td>
<td>87.8%</td>
<td>74.7%</td>
</tr>
</tbody>
</table>

TIP score all appear to have limited supporting/validation data and variable strengths and weaknesses. If using a RAM, clinicians should focus on consistency and serial audit to ensure appropriate use of the RAM, proportional use of thromboprophylaxis, patient outcomes and national benchmarking. For transparency and comparison, an example score sheet for each of the four RAMs previously mentioned can be found in online supplementary figures S1-S4.

Do these patients need blood tests prior to commencement of LMWH?
National guidelines from the British Committee for Standards in Haematology (BCSH) are clear that any patient receiving any form of heparin should have an estimate of baseline renal function and platelet count recorded. These tests have a clear rationale: ensuring appropriate dosing and agent choice, absence of coagulopathy and recording baseline platelet count to clarify the degree of any future drop. These tests are equally necessary prior to commencement on any DOAC agent. The same BCSH guidance clarifies that adverse events such as HIT are rare enough with prophylactic dose LMWH that further routine platelet counts are unnecessary, and repeat testing should be based only on clinical concern.

How long should these patients remain on prophylactic anticoagulation and who should follow them up?
The vast majority of the trial data pertaining to these patients continued prophylactic anticoagulation for the duration of immobilisation in plaster and until return to baseline mobility. This often constitutes a period of 4–6 weeks. However, with the advent of newer immobilisation strategies and virtual fracture clinics, it is becoming clear that many patients are being encouraged to mobilise early after injury and often return to weight-bearing status and full mobility earlier than initially predicted. As such, it is vital that orthopaedic teams have an interest in this issue; decisions to remove a plaster cast and encourage mobilisation may facilitate earlier cessation of thromboprophylaxis. In addition, bleeding problems early in management may adjust the risk/benefit profile.

How do I use SDM in this context?
SDM involves the clinician offering options and describing their risks and benefits, the patient expressing his or her preferences and values, and then both jointly agreeing on a treatment decision. Emergency physicians appear supportive of this approach, and a number of tools have been developed, or are being developed, to support SDM in emergency care. RAMs such as the Plymouth rule have been designed to allow potential completion by patients and to guide subsequent informed discussion. However, we are not aware of any published decision tools specifically incorporating SDM relevant to thromboprophylaxis in lower limb immobilisation. Data presented here could be used to support SDM and to develop such a tool.

Cases: outcome
Case 1
This patient has both temporary and permanent risk factors for VTE. Her age and BMI are also of concern. She has a Plymouth score of 4 and an L-TRIP(cast) score of 10 and would meet GEMNet criteria for recommendation of thromboprophylaxis. As such, she should be counselled regarding her acutely increased risk of VTE. She should be informed that her absolute risk is likely to be higher than 2%.

Funding

REFERENCES

10. Madeen R, Roberts C. Personal communication, personal email regarding the use of DOAC medications as thromboprophylaxis for patients in lower limb plaster, as well as description of recent section 28 recommendation by coroner to avoid future deaths that risk assessment and thromboprophylaxis for this indication become mandatory 2019.


