Evidence-based guidelines for thromboprophylaxis in patients with lower limb trauma requiring immobilization: an urgent, unmet need

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Lower limb immobilization is a well-known risk factor for venous thromboembolism (VTE) accounting for up to 3% of all cases in previous registry data [1]. However, recommendations and practices strongly vary from one country to another and perhaps from one emergency physician to another [2–4].

The core reason for such variation appears to be limited evidence base on pharmacological thromboprophylaxis in this population of patients with lower limb trauma requiring immobilization. In 2014, Testroote *et al.* [5] performed a comprehensive systematic review and meta-analysis, published in the Cochrane database. They found only six studies comprising 1490 patients, and only half of which (n = 788) were non-operative cases. Their results suggested that prophylactic dose low molecular weight heparin (LMWH) could be clinically effective, reporting a reduction in asymptomatic and symptomatic deep vein thrombosis in this population. No statistically significant reduction was seen in cases of pulmonary embolism. Since this publication, several further randomised trials have been conducted on this topic; and the largest of which (POT-CAST), failed to confirm the clinical effectiveness of LMWH versus no treatment [6]. In this pragmatic open-label, controlled, randomized study including 1519 patients, symptomatic VTE occurred in 1.4% with treatment versus 1.8% in the control group [relative risk 0.8; 95% confidence interval (CI) 0.3–1.7] [6]. An updated systematic review including POT-CAST (amongst others) and comprising 3680 patients continued to suggest that LMWH was effective at reducing the odds of symptomatic VTE when compared to control (OR 0.40, 95% CI 0.21–0.76) [7]. However, the quality of the included evidence ranged from low to moderate, due to the heterogeneity of the inclusion criteria and variable definitions of disease. Therefore, the authors' conclusion was that 'future research might give more directives on specific thromboprophylaxis advice for different patients or patient groups, based on patient and trauma characteristics'. This conclusion has been echoed in recent works and leads to two specific unresolved questions for patients with lower-limb trauma and immobilization: (1) Who are the patients at low risk of VTE who can safely avoid pharmacological thromboprophylaxis? (2) For at-high risk of VTE, what anticoagulant treatment option is likely to be best?

Regarding the first question, some risk assessment models (RAMs) have been proposed [8]. Several of these models have undergone attempted external validation in retrospective cohort. The Leiden-TRiP(cast) score was derived using multivariate logistic regression to identify risk factors within a case-control study data set (MEGA study) and was retrospectively validated in two other cohorts [9]. The Trauma, Immobilization and Patient (TIP) score was built by an international expert consensus using the Delphi method and was retrospectively validated in the MEGA cohort [10]. Finally, as most of the clinical variables (apart from trauma characteristics) of the Leiden-TRiP(cast) score were included by the experts in the TIP score, the authors developed and validated a new combined and simplified version: the TRiP(cast) score (for Thrombosis Risk Prediction following cast immobilization). This score includes 14 predictors related to trauma severity, degree of immobilization and patients' characteristics each rated from 1 to 4 (Nemeth *et al.*, in press). The external validity of the TRiP(cast) score to define a subgroup of patients at low risk of VTE not requiring thromboprophylaxis (i.e. patients with TRiP(cast) score <7) will be assessed in the CASTING study, an interventional cluster randomized study (NCT04064489). As yet, no RAM has been externally validated in a prospective cohort.

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One unintended result of the POT-CAST study was the identification of high symptomatic VTE risk certain patients, despite use of LMWH for thromboprophylaxis. With retrospective application of the TRiP(cast) score, recent work suggests patients with a score ≥7 and <12 and patients with a score >12 had a 3-month symptomatic VTE risk of 2% and 10%, respectively (Nemeth *et al*., in press). These rates appear unacceptable and may justify more aggressive thromboprophylactic regimens in higher risk patients. Higher weight adjusted doses of LMWH warrant further study. In addition, two studies have assessed fondaparinux for this indication and shown promising results [11,12]. In a recent systematic review with network meta-analysis, the odds ratio for symptomatic VTE with fondaparinux was 0.11 (95% CI 0.01–0.94) versus 0.40 (95% CI 0.12–0.99) with LMWH. The probability of fondaparinux being the most effective treatment was 0.91 [13]. This analysis also suggests that there may be differences in the efficacy between the different types of LMWH. Lastly, it is well known that LMWH and fondaparinux required daily subcutaneous injections which may negatively impact on patients' quality of life and compliance. Direct oral anticoagulant options for thromboprophylaxis have proven to be at least as efficient as LMWH for inpatients undergoing major orthopaedic surgery [14]. However, to our knowledge, no randomized controlled study has been performed to assess their efficacy and safety in patients with lower-limb trauma and orthopaedic immobilization. Current work is underway in China, albeit exclusively in patients with immobilisation following operative intervention (NCT04128254).

Pending the validation of RAMs and personalised thromboprophylaxis strategies, what would we recommend? Individualized risk stratification and shared decision making should be our goal. A local protocol established with the involvement of emergency physicians, orthopaedic surgeons, specialists in thrombosis and hemostasis, etc. may be an efficient way to share expertise and improve the reliability of local practice. Several RAMs are available to aid physicians in evaluation of the VTE risk and help decision-making, especially to define low-risk patients who may not require treatment. However, in the absence of definitive evidence, the decision on thromboprophylaxis should be shared with the patient. This discussion should take into account his/her own assessment of the benefits, risks, cost and burdens of such treatment. Such discussion has multiple benefits: it is likely to promote adherence and satisfaction, but will also serve to provide clear information on risk and safety netting, such that patients with developing symptoms will recognize them early and seek appropriate medical attention [15]. Finally, whenever possible, offering patients with lower-limb trauma and immobilization the chance to participate in a clinical trial is undoubtedly the best way to develop the evidence base and improve patients care.

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Conflicts of interest

There are no conflicts of interest.

References

1 Bertoletti L, Righini M, Bounameaux H, López-Jiménez L, Tiraferri E, Visonà A, Monreal M; RIETE Investigators. Acute venous thromboembolism after non-major orthopaedic surgery or post-traumatic limb immobilisation. Findings from the RIETE registry. *Thromb Haemost* 2011; **105**:739–741.

2 Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, *et al*. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141**:e278S–e325S.

3 Samama CM, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, *et al*.; French Society of Anaesthesia and Intensive Care. [French society of anaesthesia and intensive care. Guidelines on perioperative venous thromboembolism prophylaxis. Update 2011. Short text]. *Ann Fr Anesth Reanim* 2011; **30**:947–951.

4 Roberts C, Horner D, Coleman G, Maitland L, Curl-Roper T, Smith R, *et al*. Guidelines in emergency medicine network (gemnet): guideline for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation. *Emerg Med J* 2013; **30**:968–982.

5 Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev* 2008; **8**:CD006681.

6 van Adrichem RA, Nemeth B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, *et al*.; POT-KAST and POT-CAST Group. Thromboprophylaxis after knee arthroscopy and lower-leg casting. *N Engl J Med* 2017; **376**:515–525.

7 Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. *Cochrane Database Syst Rev* 2017; (8):CD006681.

8 Horner D, Goodacre S, Pandor A, Nokes T, Keenan J, Hunt B, *et al*. Thromboprophylaxis in lower limb immobilisation after injury (tilli). *Emerg Med J* 2020; **37**:36–41.

9 Nemeth B, van Adrichem RA, van Hylckama Vlieg A, Bucciarelli P, Martinelli I, Baglin T, *et al*. Venous thrombosis risk after cast immobilization of the lower extremity: derivation and validation of a clinical prediction score, L-trip(cast), in three population-based case-control studies. *Plos Med* 2015; **12**:e1001899; discussion e1001899.

10 Douillet D, Nemeth B, Penaloza A, Le Gal G, Moumneh T, Cannegieter SC, Roy PM. Venous thromboembolism risk stratification for patients with lower limb trauma and cast or brace immobilization. *PLoS One* 2019; **14**:e0217748.

11 Samama C, Lecoules N, Kierzek G, Claessens Y, Riou B, Rosencher N, *et al*. Comparison of fondaparinux with low-molecular-weight heparin for VTE prevention in patients requiring rigid or semi-rigid immobilization for isolated non-surgical below-knee injury. *J Thromb Haemost* 2013; **11**:1833–1843.

12 Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ; PROTECT studygroup. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. *Injury* 2017; **48**:936–940.

13 Horner D, Stevens JW, Pandor A, Nokes T, Keenan J, de Wit K, *et al*. Pharmacological thromboprophylaxis to prevent venous thromboembolism in patients with temporary lower limb immobilization after injury: systematic review and network meta-analysis. *J Thromb Haemost* 2019; jth.14666.

14 Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012; **344**:e3675.

15 Hess EP, Grudzen CR, Thomson R, Raja AS, Carpenter CR. Shared decision-making in the emergency department: respecting patient autonomy when seconds count. *Acad Emerg Med* 2015; **22**:856–864.