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# Thromboembolic risk stratification by TRiP(cast) score to rationalise thromboprophylaxis in patients with lower leg trauma requiring immobilisation: a study protocol of the casting stepped-wedge cluster randomised trial

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## ABSTRACT

**Introduction** Patients with lower limb trauma requiring orthopaedic immobilisation may be at risk of venous thromboembolism but opinions differ about who may benefit from thromboprophylactic anticoagulant treatment. The aim of this CASTING study is to demonstrate the safety of thromboprophylaxis based on the Thrombosis Risk Prediction for patients with cast immobilisation (TRiP(cast)) score with regards to the 3-month incidence of symptomatic venous thromboembolism events in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment in comparison to current practice.

**Methods and analysis** CASTING will be a stepped-wedge cluster randomised controlled clinical trial, performed in 15 emergency departments in France and Belgium. With their informed consent, outpatients admitted to one of the participating emergency departments for a lower limb trauma requiring orthopaedic immobilisation without surgery will be included. All centres will begin the trial with the 'observational period' and, every 2 weeks, 1 centre will be randomly assigned to switch to the 'interventional period' and to apply the TRiP(cast) score, in which only patients with a score ≥7 will receive thromboprophylactic anticoagulant treatment. The primary endpoint is the rate of clinical thromboembolic events within 90 days following the inclusion of low-risk patients not receiving thromboprophylaxis.

**Ethics and dissemination** The protocol has been approved by the Comité de Protection des Personnes Sud I (Ethics Review ID-RCB: 2019-A01829-48) for France and the Comité d'éthique hôpital-facultaire Saint Luc (N° B403201941338) for Belgium. It is carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

**Trial registration number** NCT04064489.

## Strengths and limitations of this study

- The CASTING study will be the first prospective study evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation.
- The CASTING trial will be a prospective stepped-wedge randomised clinical trial in 15 emergency departments in France and Belgium.
- A medico-economic analysis will be carried out to demonstrate the efficiency of this strategy.
- Due to the design, the study staff and participating investigators are not blinded to the period which is a limitation.

## INTRODUCTION

Lower limb traumas requiring orthopaedic immobilisation (plaster or splint) without surgery are a common reason for admission to the emergency department (ED). In Australia, for example, over 90 000 ankle and/or foot soft tissue injuries were recorded in 2014–2015.[1] Due to venous stasis caused by immobilisation, hypercoagulable states and vascular injuries brought on by the trauma, these patients are at risk of developing venous thromboembolism (VTE).[2] The OR of developing deep venous thrombosis (DVT) or pulmonary embolism (PE) following immobilisation with a cast boot is estimated to be 8.3 (95% CI 5.3 to 12.9) after adjusting for age, gender, body mass index and levels of regular physical activity.[3] Moreover, in patients immobilised using cast boots, the risk is higher if the indication is

traumatic rather than non-traumatic: OR 12.7 (95% CI 6.6 to 24.6) versus 7.6 (95% CI 0.9 to 66.4).[3] For this reason, the current practice in many countries, and especially in France and Belgium, is to prescribe thromboprophylaxis for the majority of patients with lower limb trauma and orthopaedic immobilisation.[4 5] Indeed, the efficacy (including asymptomatic thromboembolism and distal DVT) of low molecular weight heparin (LMWH) and fondaparinux has been shown in selected patient populations.[6–8] However, the risk/benefit ratio of this treatment is still controversial.[9 10] The largest randomised controlled study on the subject did not show any benefit of LMWH on the rate of symptomatic VTE among 1435 non-selected patients. VTE occurred in 10 of the 719 patients (1.4%) in the treated group and in 13 of the 716 patients (1.8%) in the control group (absolute difference in risk −0.4%; 95% CI −1.8% to 1.0%).[11] Moreover, the cost of this therapy is considerable. Therefore, in 2017, the Cochrane meta-analysis concluded that a stratification of thromboembolism risk was required[1] in order to identify high-risk patients with lower leg cast immobilisation who may benefit from thromboprophylaxis and low-risk patients who will not.[12–14]

Risk assessment models have been developed to establish the individual VTE risk of each patient.[5 15 16] The L-TRiP(cast) (Leiden-Thrombosis Risk Prediction for patients with cast immobilisation) score was developed in the Netherlands, using data from a large population-based case–control study.[15] It was retrospectively validated in two independent datasets. The TRiP(cast) score was developed using a very different approach that is, an international panel of experts and professionals using the Delphi consensus method and validated in a large case–control cohort (MEGA study).[5] Thanks to an international collaboration, we recently developed and validated a combined and simplified version of the two earlier prediction models developed for VTE risk following lower limb immobilisation: the TRiP(cast) score[16] (table 1). This is made up of 14 variables: the trauma severity, the kind of immobilisation and 12 variables related to the patient's characteristics. The TRiP(cast) score is easy to calculate, thanks to a digital application developed for IOS and the Android mobile platform (14). In external validation on the Prevention of Thrombosis after Lower Leg Plaster Cast (POT-CAST) database, it exhibited an area under the curve of 0.74 (95% CI 0.61 to 0.87). The calibration plot confirmed a good correspondence between the observed and predicted risks (intercept 0.0016 and slope 0.0933). Using a cut-off score of 7, the sensitivity, specificity, positive and negative predictive values were 76.1%, 51.2%, 2.5% and 99.2%, respectively. With this cut-off, it is possible to identify a large group of patients at very low risk of developing VTE. In the validation dataset, low-risk patients (score <7) represented 50.7% (n=728/1435) of the total patients and their observed symptomatic VTE risk was 0.8% (95% CI 0.3 to 1.7). Conversely, high-risk patients (score ≥7)

**Table 1** TRiP(cast) score*

| Trauma† | Points |
|---|---|
| High-risk trauma | 3 |
| Fibula and/or tibia shaft fracture | |
| Tibial plateau fracture | |
| Achilles tendon rupture | |
| Intermediate-risk trauma | 2 |
| Bi or tri-malleolar ankle fracture | |
| Patellar fracture | |
| Ankle dislocation, Lisfranc injury | |
| Severe knee sprain (with oedema/haemarthrosis) | |
| Severe ankle sprain (grade 3) | |
| Low-risk trauma | 1 |
| Single malleolar ankle fracture | |
| Patellar dislocation | |
| (Meta)tarsal bone(s) or forefoot fracture | |
| Non-severe knee sprain or ankle sprain (grade 1 or 2) | |
| Significant muscle injury | |
| Immobilisation‡ | |
| Upper-leg cast | 3 |
| Lower-leg cast | 2 |
| Foot cast (ankle free) or any semi-rigid cast without plantar support | 1 |
| Other cast or bracing with plantar support | 0 |
| Patient characteristics§ | |
| Age <35 years | 0 |
| Age ≥35 years and <55 years | 1 |
| Age ≥55 years and <75 years | 2 |
| Age ≥75 years | 3 |
| Male sex | 1 |
| BMI ≥25 kg/m$^2$ and <35 kg/m$^2$ | 1 |
| BMI ≥35 kg/m$^2$ | 2 |
| Family history of VTE (first-degree relative) | 2 |
| Personal history of VTE or known major thrombophilia | 4 |
| Current use of oral contraceptives or oestrogenic hormone therapy | 4 |
| Cancer diagnosis within the past 5 years | 3 |
| Pregnancy or puerperium | 3 |
| Immobilisation (other) within the past 3 months¶ | 2 |
| Hospital admission, bedridden or flight >6 hours and lower limb paralysis | |
| Surgery within the past 3 months | 2 |
| Comorbidity | 1 |
| Heart failure, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease and inflammatory bowel disease | |
| Chronic venous insufficiency (varicose veins) | 1 |

*TRiP(cast) score is the sum of the Trauma, Immobilisation and Patient component scores.
†Trauma: choose one (the most severe trauma).
‡Immobilisation: choose one.
§Patient: multiple points can be scored.
¶Other immobility next to cast immobilisation.
BMI, body mass index; TRiP(cast), Thrombosis Risk Prediction for patients with cast immobilisation score; VTE, venous thromboembolism.

represented 49.3% (n=707/1435) of the total patients and their observed symptomatic VTE risk was 2.5% (95% CI 1.6 to 4.0). Among low-risk patients treated with LMWH, 0.4% (1.3/360) developed symptomatic VTE as compared with 1.1% (4.2/367.8) in untreated patients: relative risk of 0.30 (95% CI 0.03 to 2.60).[16] In a French monocentric prospective study, this subgroup corresponded to 70% of patients with lower limb trauma and orthopaedic immobilisation.[5]

### Aim and hypothesis

The aim of the CASTING study is to demonstrate, in patients with lower limb trauma requiring orthopaedic immobilisation and admitted to the ED, the safety of thromboprophylaxis based on the TRiP(cast) score with regards to the 3-month rate of symptomatic VTE in low-risk patients not receiving thromboprophylaxis, as well as the usefulness of this strategy on the rate of patients receiving anticoagulant treatment as compared with current practice.

## METHODS AND ANALYSIS

### Study design

The CASTING trial will be a prospective stepped-wedge randomised clinical trial in France and Belgium.[17]

### Trial objectives and outcomes

#### Primary objective and outcome

The main objective will be to demonstrate the reliability and the safety of a TRiP(cast) score of <7 in order to not consider thromboprophylaxis for emergency patients with lower limb trauma requiring orthopaedic immobilisation without surgery. The primary outcome will be the rate of symptomatic VTE events (objectively confirmed DVT or PE, fatal PE and unexplained sudden death) during the 3-month follow-up period among patients with a TRiP(cast) score of <7 without thromboprophylaxis. The TRiP(cast) score will be considered reliable if the rate of VTE is lower than or equal to 1%, with an upper limit of the 95% CI lower than or equal to 2% (non-inferiority hypothesis). An independent adjudication committee will assess all potential clinical events centrally, confirm or deny their occurrence and decide on their severity. Final assignments of the suspected symptomatic VTE, suspected major bleeding or suspected non-major clinically relevant bleeding will be based on the consensus of the independent adjudication committee of clinical events.[18] Members of the adjudication committee are experienced clinicians independent from the investigators and the sponsor.

#### Secondary objectives

The first secondary objective will be to demonstrate that the implementation of the TRiP(cast) score during the interventional period significantly reduces the rate of patients receiving thromboprophylaxis compared with current practice during the observational period.

The other secondary objectives will be to compare current practice (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period):

1. The rate of symptomatic VTE at 90 days.
2. The rate of major bleeding according to the criteria proposed by the International Society on Thrombosis and Haemostasis.[19]
    1. Fatal bleeding.
    2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.
    3. Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.
3. The rate of non-major clinically relevant bleeding is defined as any bleeding requiring hospitalisation or a medical intervention, including temporary withholding of anticoagulant treatment, to stop the bleeding at 90 days.

Finally, we will perform a medico-economic analysis between current practice (observational period) and thromboprophylaxis based on the TRiP(cast) score (interventional period) within 90 days of inclusion, focusing on the cost–utility ratio in terms of cost per quality-adjusted life year gained (primary analysis) and the cost-effectiveness ratio in terms of cost per symptomatic VTE avoided (secondary analysis).

### Experimental plan for the stepped-wedge design

In this stepped-wedge clinical trial, patients will be recruited in 15 EDs in France and Belgium, from academic and non-academic centres, and from rural and urban communities (table 2). All centres will begin the trial with the 'observational period' and every 2 weeks, 1 centre will be randomly assigned to switch to the 'interventional period' and to apply the TRiP(cast) score. After 32 weeks, all centres will be in the 'interventional period' for the 7 months of the trial remaining (table 3). The order of centres changing to the interventional phase will be developed using non-stratified list randomisation. This randomisation will be carried out by the methodological managers of the Research and Innovation Department of Angers University Hospital (including the data management). The inclusion rate will be closely monitored during the trial, and time periods will be adjusted if the number of patients included differs substantially from expectation in order to respect the number of subjects required in the observational phase.[20] No data monitoring committee has been set up, as this is not a drug study but an implemented strategy. A monitoring grade has been defined according to the risk of the study according to the promoter's procedures (ie, grade 1: low level of risk).

This design was chosen for the following reasons:

Table 2 List of the principal Investigators of participating centres

| Surname | First name | Country | Hospital |
|---|---|---|---|
| Baudin | Laure | France | CH Cholet |
| Brice | Christian | France | CH St Brieuc |
| Casalino | Enrique | France | APHP Paris, Bichat |
| Douillet | Delphine | France | CHU Angers |
| Dumas | Florence | France | APHP Paris, Cochin |
| Balen | Frédéric | France | CHU Toulouse |
| Viglino | Damien | France | CHU Grenoble |
| Malet | Anne | France | CHRU Orléans |
| Marjanovic | Nicolas | France | CHU Poitiers |
| Montassier | Emmanuel | France | CHU Nantes |
| Penaloza | Andrea | Belgium | Bruxelles, Universités cliniques Saint-Luc |
| Polisset | Nathalie | France | CHU Tours |
| Schotté | Thibault | France | CH Le Mans |
| Soulat | Louis | France | CHU Rennes |
| Vives | Philippe | France | CH Agen |

- The comparison with current practice was chosen because of the lack of updated recommendation and consensus guidelines on thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation. Indeed, the 2012 US recommendations advised against systematic preventative treatment if the patient does not require surgery, whereas the 2011 French guidelines suggest thromboprophylaxis for all patients without possible foot support if there is not a high risk of bleeding.[21 22] Therefore, the decision to introduce thromboprophylaxis varies from country to country, from centre to centre and even from doctor to doctor.[4]
- Comparison to current practice precludes randomisation at the patient level or a crossover design that would induce bias through contamination. The implementation of the score will change healthcare practices and an emergency physician who would have used the TRiP(cast) score during the study will be influenced by the score criteria and will change his/her 'standard of care' in deciding on thromboprophylaxis.
- A cluster, stepped-wedge design prevents such contamination and also prevents a potential 'period effect' that could have resulted from a simple before/after design.
- This design is especially suited for EDs because it is less time-consuming than randomisation at the patient level, as the physician knows, prior to patient inclusion, what he/she will do if the patient agrees to participate in the study.
- The robustness of the stepped-wedge design is widely recognised[23 24] and this methodology is increasingly used in studies aimed at implementing changes in care practices.[17]

## Study settings and population

The CASTING trial will involve patients with isolated lower limb trauma requiring rigid (plaster or resin) or semi-rigid immobilisation for an anticipated duration of at least 7 days. It will be a continuous recruitment process. Therefore, consecutive adult patients who are admitted for this reason to one of the participating EDs will be assessed for inclusion. They must have up-to-date health insurance coverage and express in writing their consent to participate in the study after verbal and written explanations of the procedure, as recommended in clinical and research good practices (online supplemental file 1). If the patient is unable to consent, then the physician will seek consent from a trusted person, family member or close relative. If none is available, the physician can proceed to an 'emergency inclusion' without prior consent. Therefore, and as soon as possible, a written informed consent to pursue study participation will be requested of the patient or a trustworthy person as soon as possible. In case of refusal, the patient will be excluded from the trial (L1122-1-2 article of the French Public Health Code).

Patients will be excluded if they have any of the following:

- Current anticoagulant treatment at time of trauma.
- Trauma requiring surgery or hospitalisation for more than 2 days (excluding short-term hospital stay) at time of inclusion.
- Comorbidity or comorbidities requiring hospitalisation at time of inclusion.
- Any factor that makes 90-day follow-up impossible.
- Legal protection measures (tutorship or curatorship) or detainee status.

## Description of the intervention

In both study periods, patients admitted for lower limb trauma requiring rigid or semi-rigid immobilisation without surgery will be evaluated for potential inclusion. After verifying eligibility and obtaining patient consent, the investigator will proceed to inclusion. The patient's characteristics, including thromboembolism risk factors, the kind of trauma and the type of immobilisation, as well as the anticipated duration of immobilisation will be collected. The data will be recorded in an electronic case report form (e-CRF), available on smartphones, tablets and computers and secured by a personal password. All personal data will be subsequently anonymised. All patients included will receive a study participation card, including emergency phone numbers and the phone number of the local principal investigator of the trial (online supplemental file 2). Participants may not participate in any other intervention trial during the CASTING study participation period.

**Table 3** Experimental design of the stepped-wedge methodology

| | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 | Step 7 | Step 8 | Step 9 | Step 10 | Step 11 | Step 12 | Step 13 | Step 14 | Step 15 | Step 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Centre 1 | C | I | I | I | I | I | I | I | I | I | I | I | I | I | I | I |
| Centre 2 | C | C | I | I | I | I | I | I | I | I | I | I | I | I | I | I |
| Centre 3 | C | C | C | I | I | I | I | I | I | I | I | I | I | I | I | I |
| Centre 4 | C | C | C | C | I | I | I | I | I | I | I | I | I | I | I | I |
| Centre 5 | C | C | C | C | C | I | I | I | I | I | I | I | I | I | I | I |
| Centre 6 | C | C | C | C | C | C | I | I | I | I | I | I | I | I | I | I |
| Centre 7 | C | C | C | C | C | C | C | I | I | I | I | I | I | I | I | I |
| Centre 8 | C | C | C | C | C | C | C | C | I | I | I | I | I | I | I | I |
| Centre 9 | C | C | C | C | C | C | C | C | C | I | I | I | I | I | I | I |
| Centre 10 | C | C | C | C | C | C | C | C | C | C | I | I | I | I | I | I |
| Centre 11 | C | C | C | C | C | C | C | C | C | C | C | I | I | I | I | I |
| Centre 12 | C | C | C | C | C | C | C | C | C | C | C | C | I | I | I | I |
| Centre 13 | C | C | C | C | C | C | C | C | C | C | C | C | C | I | I | I |
| Centre 14 | C | C | C | C | C | C | C | C | C | C | C | C | C | C | I | I |
| Centre 15 | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | I |

Each step lasts for 2 weeks, except for step 1, which last for 4 weeks, and step 16, which last 7 months.

C, Control; I, Intervention.

### Observational control period

During this period, the TRiP(cast) score will not be calculated. Physicians will be free to decide whether or not to prescribe thromboprophylactic treatment with LMWH or fondaparinux depending on local practice. To avoid contamination bias, the first question of the CRF is whether or not the physician-in-charge has considered preventive anticoagulation. They can fill the TRiP(cast) score variables into the CRF only when they have answered this question.

### Interventional period

During this period, the TRiP(cast) score will be prospectively calculated and the use of thromboprophylactic treatment will be based on its result. When the emergency physician records the patient's data on the e-CRF, the TRiP(cast) score will be automatically calculated. The physician will be advised to prescribe LMWH or fondaparinux if the score is 7 or higher, otherwise not to introduce thromboprophylaxis (score <7). According to the preference of individual hospitals and national recommendations, the following four treatments could be used, all as one daily subcutaneous injection: enoxaparin 40 mg, nadroparin 2850 IU, dalteparin 2500 IU or fondaparinux 2.5 mg.

### Follow-Up

In both periods, the patients included will receive a follow-up consultation by phone at 30 days and 90 days after inclusion, in order to collect data on potential clinical events (thromboembolic events, haemorrhages, thrombocytopenia or other adverse effects), and on the use of healthcare resources linked to thromboprophylaxis (anticoagulant treatments, biological examinations, medical consultations or subsequent hospitalisations). The phone interviews will be performed using a standardised follow-up form at each centre.

An independent adjudication committee will assess all potential clinical events in order to confirm their occurrence and decide on their severity.

## Statistical analysis

### Descriptive analysis

Quantitative variables will be described in terms of mean±SD in cases of Gaussian distribution. Otherwise, they will be described in terms of median and IQR. Qualitative variables will be described in terms of numbers and frequencies. A comparison of patient characteristics between the two referral strategies will be evaluated using the Student's t-test, Mann-Whitney U test or Fisher's exact test, depending on the context.

### Main objective

The main analysis will be conducted on patients enrolled during the interventional period and who will not receive a thromboprophylactic anticoagulant treatment because of a TRiP(cast) score <7. The rate of symptomatic VTE that occurred between ED discharge and the 3-month follow-up and its 95% CI will be estimated using a logistic mixed model with a random effect on centre. The TRiP(cast) score will be considered reliable if the upper 95% confidence limit of VTE rate is less than 2%. A sensitivity analysis will be performed as an intention-to-treat analysis taking into account all patients with a TRiP(cast) score <7.

### Secondary objectives

The first secondary outcome will be analysed on the 'intention-to-treat' population, meaning all evaluable patients included in the observational period versus all evaluable patients included in the interventional period. A logistic mixed model with a random effect on centre will be conducted, which will allow the intracluster and intercluster correlations to be taken into account. A two-sided test with a type I error rate of 5% will be conducted.

The 90-day incidence of symptomatic VTE (including fatal PE and unexplained sudden deaths), major bleeding (including fatal bleeding) and non-major clinically relevant bleeding during the control period and the interventional period will be compared using the same method.

The results will be presented as the absolute difference in rates between the two periods and their 95% CI.

### Sensitivity analyses

Sensitivity analyses will be performed excluding patients from centres with a mean rate of inclusion by month below 5.

All the analyses will be conducted using R software (R Core Team, 2018, a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

### Missing data

No imputation of missing data is planned. However, missing data will be analysed to determine whether they are informative and whether they are likely to lead to potential selection or information bias.

### Multiple testing

A hierarchical management of objectives will be carried out, making it possible to limit the problem of multiplicity. Moreover, when necessary, a correction will be made allowing a control of the Family-Wise Error Rate (FWER) at a risk of 5%.

Trial results will be reported in accordance with the extended Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for cluster randomised trials.

## Sample size calculation

Taking a 1% rate of symptomatic VTE in the low-risk group of patients,[2] 753 patients would be required to obtain a higher limit of the 95% CI that is lower than or equal to 2%. In the POT-CAST trial, the proportion of low-risk patients according to the TRiP(cast) score (<7) was 51%. However, only patients with rigid immobilisation were included.[11] In the CASTING study, we will include immobilised patients with either a rigid or semi-rigid splint or

brace, and, conversely, patients requiring surgery at inclusion will be excluded. In a monocentric study conducted in Angers, the proportion of low-risk patients according to the TRiP(cast) score (<7) was 67%.[5] Considering that this rate would be ≥60% in the population included in the CASTING study and the possibility of patients lost to follow-up or patients who cannot be analysed at 5%, the number of patients to include in the trial has been set at 1400 in the interventional period with a type I error rate of 5% and a power of 80%.

The number of patients to be included in the observational period has been established from the first secondary objective. Considering a 15% difference in the rate of patients receiving prophylactic anticoagulant treatment during the interventional period versus the control period, participation of 15 centres and an intraclass correlation coefficient (centre effect) of 0.1, 540 patients would be needed at each stage to demonstrate a significant difference with a 5% α risk and power of 80%. Taking into account the possibility of patients lost to follow-up and patients who cannot be analysed, the number of patients to be included in the control observational period was set at 600.

The total number of participants in the study has thus been set at 2000 patients across 15 centres.

### Patient and public involvement

The current trial will be conducted without direct patient involvement. The ethics committee (Comité de Protection des Personnes Sud I) includes patient representatives, charged with the responsibility of protecting patient rights; thus, the CASTING trial protocol was reviewed by a patient representative. Besides the above review process, patients will not be invited to comment on the study design and interpretation of the study results. Patients were not involved in the writing of this manuscript.

## ETHICS AND DISSEMINATION

Informed consent will be obtained from all study participants whenever possible. If the patient is unable to consent, informed consent from a relative will be obtained. An institutional review board has authorised the study (Comité de Protection des Personnes Sud I, ID-RCB: 2019-A01829-48, 16 October 2020) for all participating centres and authorisation was granted by the ethics committee of the participating hospital in Belgium (Comité d'éthique hôpital-facultaire Saint Luc, N° B403201941338). The trial has been designed on the basis of the SPIRIT guidelines and Standard Protocol Items.[25] A SPIRIT checklist file is attached (online supplemental file 3).

The results of this study will be published in peer-reviewed manuscripts and will be presented to local community groups and stakeholders, as well as at national and international conferences as applicable. The authorship guidelines[26] will be followed for all relevant publications and presentations. Open access publication of this protocol will facilitate full public access.

## DISCUSSION

To the best of our knowledge, this study protocol describes the first prospective, multicentric study evaluating the implementation of a risk-stratification model for thromboprophylaxis in patients with lower limb trauma and orthopaedic immobilisation.

It is based on a well-validated model, the TRiP(cast) score, which has been effective in defining low-risk patients that would not benefit from prophylactic anticoagulant treatment. If our hypotheses are confirmed, the CASTING trial will confirm that a large number of patients with lower limb trauma requiring orthopaedic immobilisation without surgery could safely not receive any thromboprophylaxis, and conversely that some patients not receiving treatment in current practice could benefit from thromboprophylaxis. Indeed, in a monocentric, observational pilot study, 35.5% (11/30) of patients classified as being at high risk of VTE according to the TRiP(cast) score did not receive preventative treatment. Among them, one patient developed a deep VTE. On the other hand, 31.5% of patients classified as being low risk (52/165) (63.3% of all patients) received thromboprophylactic anticoagulant treatment.[5] The cost of this treatment and its impact on the day-to-day life of patients, due to its subcutaneous administration, are significant. Pandor *et al* suggest that risk-based strategies are potentially more cost effective in limiting thromboprophylaxis.[9] Due to the high frequency of lower limb trauma, this represents significant healthcare costs.[27 28] By presenting a high level of evidence, thanks to the stepped-wedge design, it is possible to confirm that the implementation of the TRiP(cast) score leads to a significant decrease in the rate of patients receiving anticoagulant treatment and an improvement on the cost–utility ratio, indicating that the CASTING study will have an important impact on patient care and public health.

The results of the CASTING study are particularly highly anticipated and after the protocol was reviewed and approved by the French and Belgian ethics committees, recruitment began on 22 June 2020. The results are anticipated by the end of 2021.

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