Clinical risk assessment model to predict venous thromboembolism risk after immobilization for lower-limb trauma

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ABSTRACT

Background: Patients with lower-limb trauma requiring immobilization have an increased risk of venous thromboembolism (VTE). While thromboprophylaxis for all patients seems not effective, targeted thromboprophylaxis in high risk patients may be an appropriate alternative. Therefore, we aimed to develop and validate a risk assessment model for VTE risk: the TRiP(cast) score (Thrombosis Risk Prediction following cast immobilization).

Methods: In this prediction model study, for development, data were used from the MEGA study (case-control study into the etiology of VTE) and for validation, data from the POT-CAST trial (randomized trial on the effectiveness of thromboprophylaxis following cast immobilization) were used. Model discrimination was calculated by estimating the Area Under the Curve (AUC). For model calibration, observed and predicted risks were assessed.

Findings: The TRiP(cast) score includes 14 items; one item for trauma severity (or type), one for type of immobilization and 12 items related to patients' characteristics. Validation analyses showed an AUC of 0.74 (95%CI 0.61−0.87) in the complete dataset (n = 1250) and 0.72 (95%CI 0.60−0.84) in the imputed data set (n = 1435). The calibration plot shows the degree of agreement between the observed and predicted risks (intercept 0.0016 and slope 0.933). Using a cut-off score of 7 points in the POT-CAST trial (incidence 1.6%), the sensitivity, specificity, positive and negative predictive values were 76.1%, 51.2%, 2.5%, and 99.2%, respectively.

Interpretation: The TRiP(cast) score provides a helpful tool in daily clinical practice to accurately stratify patients in high versus low-risk categories in order to guide thromboprophylaxis prescribing. To accommodate implementation in clinical practice a mobile phone application has been developed.

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1. Introduction

Patients with lower-limb injuries requiring immobilization, i.e. brace or casting, are at risk of venous thromboembolism (VTE). Approximately 2.0% of patients will develop VTE within 3-months following immobilization without the use of thromboprophylaxis such as low-molecular weight heparin (LMWH) [1−5]. However, applying a population-based approach by providing thromboprophylaxis for all patients is not effective [6]. Therefore, an individualized approach, i.e. targeting individual patients based on the size of their VTE risk, might be an appropriate alternative. For instance, patients with a high risk may benefit from an intensified regimen of thromboprophylaxis whereas patients with a low risk can be (safely) withheld from treatment. By doing so, both thrombosis and bleeding risk can be reduced to a minimum. Because of the high prevalence of lower-limb trauma and the significant impact of VTE in terms of morbidity, mortality and resource expenditure, targeted thrombosis prevention will have a major impact on public health [7−11].

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Research in context

Evidence before this study

Venous thromboembolism (VTE) is a common complication (occurs in about 2.0% of patients) following immobilization for lower-limb trauma. Still, guidelines are ambiguous with regards to thromboprophylaxis advice to prevent VTE in these patients. Recently, we published results of the POT-CAST trials in which we showed that a prophylactic dose of low-molecular-weight-heparin for the complete duration of cast immobilization for treatment of lower-leg trauma was not effective to prevent symptomatic VTE in all patients. An individualized approach towards VTE prevention seems therefore sensible. This way, low-risk patients can be safely withheld from treatment whereas high-risk patients could receive adequate (intensified) therapy.

Added value of this study

In this study we developed and validated a new and simplified version of two earlier developed prediction models for VTE risk following lower-limb immobilization. The new TRiP(cast) score consists of 14 predictors related to trauma severity, degree of immobilization and patients' characteristics. The TRiP(cast) score performed well in both discrimination and calibration analysis. A mobile phone application was developed to enhance its use in clinical practice.

Implications of all available evidence

The TRiP(cast) score may be a useful tool for physicians to help decide on pharmacological thromboprophylaxis therapy following lower-limb trauma requiring immobilization.

To personalize thromboprophylaxis treatment in patients with lower-limb immobilization, two specific VTE risk assessment models (RAMs) have been developed [12,13]. Furthermore, two studies published a list of predictors in which case thromboprophylaxis should be considered [14]. In 2015, the Leiden-TRiP(cast) (for Leiden-Thrombosis Risk Prediction for patients with cast immobilization score) was developed in the Netherlands [13], using data from a large population-based case-control study [15]. It includes 19 items with scores ranging from 1 to 5 and was retrospectively validated in two independent datasets. Despite promising results, the Leiden-TRiP(cast) score has some weaknesses that impair its wide implementation. Mainly, it does not include trauma severity (which has been shown to be associated with VTE risk) and absolute risks for individual patients could not be obtained because of the case-control setting [16].

Hereafter, another RAM was developed for patients with lower-limb *non-surgical* trauma requiring brace or cast immobilization, e.g. the TIP score (for Trauma, Immobilization and Patients characteristics score) [17]. The TIP score was developed using a very different approach, i.e., via an international panel of experts and professionals using the Delphi consensus method. With at least a strong consensus (>75%), 13 items for trauma, 3 for immobilization and 14 for patient characteristics were selected. While the TIP score performed well, with a total of 30 items, the usability of this model in clinical practice is questionable.

Most clinical variables of the Leiden-TRiP(cast) score had also been incorporated by the experts in the TIP score. As both scores were very similar, this allowed us to select the best features of both scores and merge them together in a single new combined score: the TRiP(cast) score for "Thrombosis Risk Prediction for patients with cast immobilization".

The main aim of this study was to develop and validate a new score, the TRiP(cast) score, to identify patients with lower-limb immobilization for trauma at low or high-risk for VTE.

2. Methods

2.1. Study methods

Fig. 1 shows the study flow-chart that presents all analyses which have been performed throughout the study. Two previous risk prediction models for VTE following cast immobilization (the Leiden-TRiP(cast) score and the TIP score) were used to create a final risk score entitled the TRiP(cast) score, note: without "Leiden". (**Step 1, Fig. 1**). The Leiden-TRiP(cast) score was developed using data from the MEGA study whereas the TIP score was developed by a group of experts using the Delphi method. Following development, the TIP score was validated in the MEGA study [13]. Thereafter, score performances were compared by the AUC, sensitivity, and specificity. Both scores had a comparable discriminative value, and many similar predictors. The main difference was the Trauma component from the TIP which was lacking in the Leiden-TRiP(cast) score. Therefore, it was decided to merge both scores into one single score (**Step 2, Fig. 1**). The performance of the final TRiP(cast) score was subsequently validated in both the MEGA study and, to obtain absolute risks, in the POT-CAST trial (Prevention of Thrombosis following CAST immobilization trial) (**Step 3, Fig. 1**) [6].

2.1.1. Formation of the final TRiP(cast) score

Appendix Table A1 compares predictors included in the TIP and Leiden-TRiP(cast) scores. Both scores were merged in a single score (the TRiP(cast) score) focussing on optimal usability in clinical practice: predictors with a low prevalence (such as pneumonia or having a history of superficial vein thrombosis) were excluded from the final score. Risk points of the final TRiP(cast) score were based on that of the previous Leiden-TRiP(cast) score because these points were based on regression coefficients obtained from a multivariate logistic regression model whereas those of the TIP score had been determined by expert opinion (Delphi Method) and considered less accurate.

2.1.2. Primary study outcome measure

A prediction model which predicts the occurrence of symptomatic VTE within 3-months following cast immobilization for lower-limb trauma. As main outcome measures, model discrimination and calibration were assessed, please see the statistical analysis section for more details.

2.2. Study design

2.2.1. MEGA study

To assess the performances of all three scores, we used data from the MEGA study. Details of this study have been published previously [15,18,19]. In short, 4956 consecutive patients aged 18−70 years with a first deep vein thrombosis (DVT), pulmonary embolism (PE), or both were recruited from six anticoagulation clinics in the Netherlands between 1 March 1999 and 31 August 2004. The diagnosis of DVT or PE was confirmed by (Doppler) ultrasonography, ventilation/perfusion scan, angiography, or spiral CT scan. The control group (*n* = 6297) consisted of partners from participating patients and other controls who were identified using a random digit dialing method; controls were frequency matched to cases with respect to sex and age. All participants completed a questionnaire on risk factors for VTE that included questions on (potential) risk factors such as trauma, immobilization (including cast immobilization and location), (orthopedic) surgery, current use of (any) medication, and comorbidity in the past year before VTE.

2.2.2. POT-CAST study

For external validation of the TRiP(cast) score, data of the POT-CAST trial were used of which details have been published previously [6]. In short, in the POT-CAST trial, patients with lower-leg injuries

Step 1: Risk scores

TIP score	**L-TRiP(cast) score**
(Delphi Method)	**(Case-control data)**

- Developed in 2017
- Validated in MEGA study (Douillet et al. PLoS One 14(6): e0217748)

- Developed in 2015 in the MEGA study and validated in two other case-control studies. (PLoS Med 12(11): e1001899)

Step 2: Development phase, using data from the MEGA study

- Compare AUC of TIP and L-TRiP(cast)
- Merge both scores into one single score (The TRiP(cast) score) by expert opinion
- Calculate AUC of TRiP(cast) score in MEGA

Step 3: Validation of the TRiP(cast) score in the POT-CAST trial

Validation analyses

- AUC, sensitivity, specificity, PPV and NPV
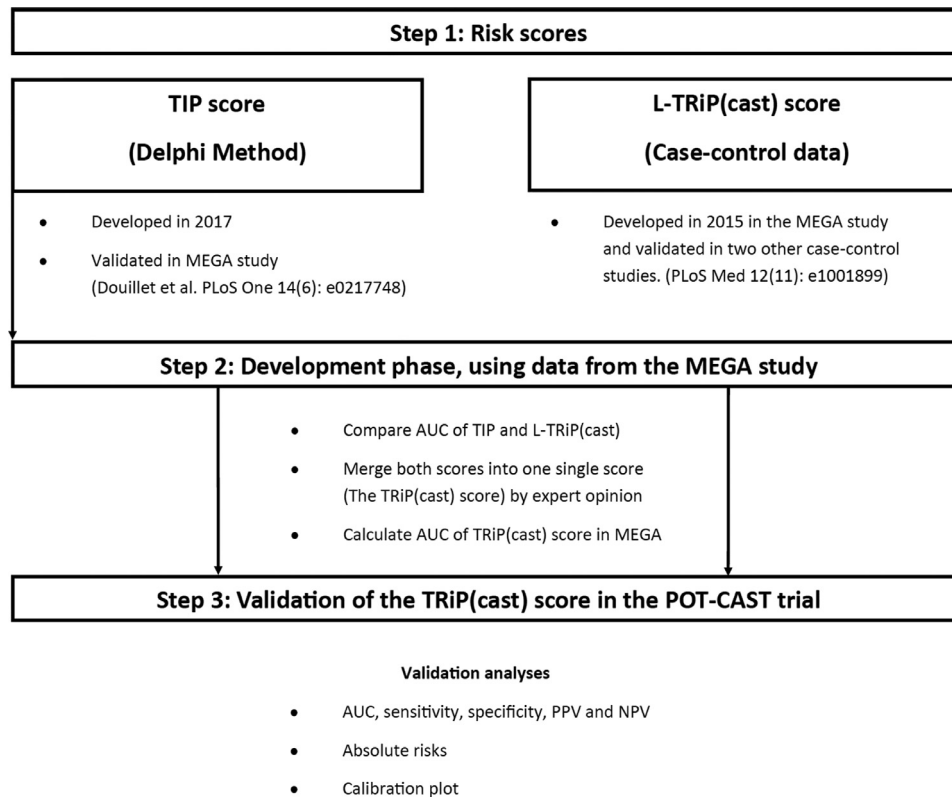- Absolute risks
- Calibration plot

Fig. 1. Flowchart of the TRiP(cast) score development and validation process.

requiring cast immobilization were randomized to receive a prophylactic dose of LMWH or no therapy during cast immobilization. To study the effectiveness of LMWH, the occurrence of symptomatic VTE within 3 months was assessed by a blinded independent outcome adjudication committee. Between March 2012 and January 2016, patients admitted to the emergency department who were aged 18 years or older were eligible for inclusion if cast immobilization of the lower-leg was indicated to treat their injury. Patients complying to one of the following criteria were excluded: history of VTE, current use of anticoagulant therapy (except antiplatelet medication), contra-indications for use of LMWH, pregnancy, mental or physical disability to fulfill study requirements or insufficient knowledge of the Dutch language. All participants completed a questionnaire on risk factors for VTE at the moment of inclusion.

Approval for both the MEGA and POT-CAST study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent.

2.3. Statistical analysis

2.3.1. Score comparison in the MEGA study

The performance of all scores was first assessed in the MEGA study. Twenty patients who underwent surgery (before or following cast-immobilization as part of their treatment) were excluded. This was done as the TIP score was originally developed for non-surgical patients only and all scores needed to be compared in the same data. In total, 179 cases and 31 controls who had cast immobilization of the lower-extremity were included. To assess model performance, the Area Under the Curve (AUC) with corresponding 95% Confidence Interval (95%CI) was estimated by means of a Receiver Operating Characteristic curve. Furthermore, the sensitivity, specificity and positive and negative predictive values (PPV and NPV) were calculated for a pre-defined cut-off (as stated in the original development papers) [13].

2.3.2. Validation of the final TRiP(cast) score in the POT-CAST trial

For the main external validation analysis of the TRiP(cast) score, we used data from all patients who were included in the intention-to-treat analysis of the POT-CAST trial (n = 1435 patients) with a cast immobilization of the lower-leg. Demographics were summarized as means $\pm$ standard deviation or proportions as appropriate. To account for missing data, we used multiple imputation techniques. Ten imputations were performed, and results were pooled according to Rubin's rules [20]. The TRiP(cast) score was thereafter calculated in all patients.

To assess model discrimination, the AUC was estimated in both the complete cases (n = 1250) and imputed data sets (n = 1435). Furthermore, the sensitivity, specificity, PPV and NPV were calculated for several dichotomized cut-off scores. To obtain estimates of absolute risks, a logistic regression analysis with VTE as dependent variable and the TRiP(cast) score as a continuous independent variable was performed. The predicted risk for each individual was calculated as follows: predicted risk = exp(a + b*TRiP(cast) score)/(1+exp[a + b*TRiP(cast) score]), with regression coefficients a and b of the logistic regression model. The predicted and observed risks for each risk score in the TRiP(cast) score were plotted against each other in a calibration plot, showing the concordance between the predicted and observed outcome. As the main aim of this study was to create and validate one final score, the Leiden-TRiP(cast) and TIP scores were not validated in the POT-CAST study. All analyses were performed in IBM SPSS Statistics for Windows, version 20.0 and Stata, version 12.

2.4. Sensitivity analyses

As the POT-CAST trial was an RCT with two different study arms (LMWH treatment and a non-treatment arm) the discriminative value (AUC) of the TRiP(cast) score was determined in both study arms separately to determine any possible treatment effect on predictive value (even though the POT-CAST trial showed non-effectiveness of LMWH).

In addition, the effectiveness of LMWH was assessed in a low and high-risk group as defined by the TRiP(cast) score (low risk <7 points, high risk ≥7 points). We calculated relative risks with corresponding 95%CI by comparing cumulative incidences of symptomatic VTE between the treated and untreated groups.

2.4.1. Development of a computerized clinical decision support system

To allow easy application of the TRiP(cast) score in clinical practice, a mobile phone application was developed for IOS (https://apps.apple.com/us/app/trip-cast-score/id1438610930) and Android mobile platforms (https://play.google.com/store/apps/details?id=com.everywhereim.tripcast&hl=nl).

2.4.2. Role of funding source

This research was funded by the Netherlands Organization for Health Research and Development, which had no role in any aspect of this study.

3. Results

3.1. Development of the final TRiP(cast) score

The final TRiP(cast) score (Table 1), consisted of 3 components (Trauma, Immobilization and Patient characteristics). A total of 14 items were included in the score: 1 for trauma severity (or type of trauma), 1 for type of immobilization and 12 items related to patients' characteristics. Note that for trauma, if there are several (i.e. ankle distortion with significant muscle injury), only the highest trauma type determines the score of the trauma component. Each item can be scored on a scale of 1 to 4 and the sum of these scores results in the TRiP(cast) score. For instance, a 50-year-old male with a BMI of 30 kg/m^2 receives 3 points (including 1 point for being older than 35 years old, 1 point for male sex and 1 point for having a BMI≥25 and <35 kg/m^2). If this patient has a bi-tri malleolar ankle fracture (2 points) requiring lower-leg cast (2 points), this results in a total of 7 points.

3.2. Risk score performances in the MEGA study

In the MEGA study, the original AUC values for the Leiden-TRiP (cast) score and TIP score were 0.78 (95% CI 0.69−0.88) and 0.77 (95%CI 0.69−0.85), respectively. The AUC of the new TRiP(cast) score was 0.77 (95%CI 0.67−0.86) (Table 2).

3.3. POT-CAST (validation) population

Among the 1435 patients included in the POT-CAST study, the TRiP (cast) score could be calculated for 1250 patients (complete predictor data). Data were imputed for 185 patients. Patient characteristics are summarized in Table 3. In brief, 49.9% were males and the mean age was 46 ± 16.5 years. The median BMI was 25.8 ± 4.5 kg/m^2. Among all patients, 9.8% had a family history of VTE, 2.5% had active cancer or cancer history within 5 years and 9.5% received oral contraceptives or hormonal therapy. The majority of patients had a fracture: 1279/1435 (89.1%). Ninety-four patients had an Achilles tendon rupture (6.6%) and thirty-five patients had an ankle distortion (2.5%). 7.0%, 8.8% and 84.2% of patients were classified as having a high, intermediate or low-risk trauma, respectively. All patients were treated with lower-leg cast and immobilized for a mean duration of 4.9 weeks ± 2.5.

Of all 1435 patients, 23 patients developed symptomatic VTE (14 had DVT, 7 had a PE, and 2 patients both) for a cumulative incidence of 1.6% (95%CI 1.3 to 2.7).

3.4. TRiP(cast) score performance

The distribution of the TRiP(cast) score among patients with or without VTE is displayed in Appendix Fig. A1. The TRiP(cast) score

Table 1
TRiP(cast) score.[a]

	Points
Trauma[b]	
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 edema/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	
Immobilization[c]	
Upper-leg cast	**3**
Lower-leg cast	**2**
Foot cast (ankle free) or any semi-rigid without plantar support	**1**
Other cast or bracing with plantar support	**0**
Patient characteristics[d]	
Age <35 years	**0**
Age ≥35 and <55 years	**1**
Age ≥55 and <75 years	**2**
Age ≥75 years	**3**
Male sex	**1**
Body Mass Index BMI ≥25 and <35 kg/m^2	**1**
Body Mass Index 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 Estrogenic hormone therapy	**4**
Cancer diagnosis within the past 5 years	**3**
Pregnancy or puerperium	**3**
Immobilization (other) within the past 3 months[e]	**2**
Hospital admission, bedridden or flight > 6 h, Lower limb paralysis	
Surgery within the past 3 months	**2**
Comorbidity	**1**
Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, IBD	
Chronic venous insufficiency *(varicose veins)*	**1**

[a] Thrombosis Risk Prediction in patients with cast immobilization score TRiP (cast) score is the sum of the Trauma, Immobilization and Patient components.
[b] Trauma: Choose one, (the most severe trauma).
[c] Immobilization: Choose one.
[d] Patient: multiple points can be scored.
[e] Other immobility next to cast immobilization.

performed well with an AUC of 0.74 (95%CI 0.61−0.87) in the complete dataset and an AUC of 0.72 (95%CI 0.60−0.84) in the imputed data set. Table 4 shows test statistics for each dichotomized cut-off of the TRiP (cast) score. For example, using a cut-off score of 7 points to stratify individuals into a low versus high-risk category (low-risk 50.7% and 49.3% high risk), the sensitivity was 76.1% and the specificity was 51.2%. Based on an incidence of VTE of 1.6% (incidence in POT-CAST), the PPV of the test (cut-off >=7 points) was 2.5%, and the NPV 99.2%.

The predicted risk (absolute VTE risk) was calculated by exp (6.677,015 + 0.3332203*TRiP(cast) score)/(1+ exp[6.677015 +

Table 2
Performance of the Leiden-TRiP(cast), TIP and TRiP (cast) score in the MEGA study.

	AUC[a]	95% CI	
Leiden-TRiP(cast) score	0.78	0.69	0.88
TIP score	0.77	0.69	0.85
TRiP(cast) score	0.77	0.67	0.86

[a] AUC denotes Area Under the Curve, CI denotes Confidence Interval.

Table 3
POT-CAST trial − validation cohort characteristics.

	Total $n = 1435$
Trauma, *n* (%)	
High-risk trauma	100 (7.0)
Intermediate-risk trauma	127 (8.8)
Low-risk trauma	1208 (84.2)
Immobilization	
Duration of lower-leg cast in weeks, mean (SD)	4.9 (2.5)
Lower-leg cast indication, *n* (%)	
Fracture	1279 (89.1)
Achilles tendon rupture	94 (6.6)
Ankle distortion	35 (2.5)
Antalgic	9 (0.6)
Contusion	13 (0.9)
Other	5 (0.3)
Fracture type, *n* (%)	
Ankle	497 (34.6)
Metatarsal	532 (37.1)
Calcaneus	56 (3.9)
Pilon tibial	3 (0.2)
Tibia and fibula shaft	3 (0.2)
Talus	50 (3.5)
Tarsal	98 (6.8)
Phalanx	23 (1.6)
Lisfranc	6 (0.4)
Other[a]	11 (0.8)
Surgery, *n* (%)[b]	170 (11.8)
Patient characteristics[c]	
Mean age (SD), years	46.0 (16.5)
Male sex, *n* (%)	719 (49.9)
Mean BMI (SD), kg/m^2	25.8 (4.5)
Smoking, *n* (%)	
Current	173 (26.1)
Ever	188 (28.4)
Family history of venous thromboembolism (1st degree), *n* (%)	140.5 (9.8)
Personal history of VTE or known major thrombophilia	Not included
Current use of oral contraceptives or Estrogenic hormone therapy	137 (9.5)
Cancer within the past 5 years or active cancer	36 (2.5)
Pregnancy or puerperium	Not included
Immobilization (other)	134.5 (9.4)
Surgery within the past 3-months	232.6 (16.2)
Comorbidity	122.9 (8.6)
Varicose veins	222.2 (15.4)

SD: standard deviation, BMI: Body Mass Index.
[a] Fractures not meeting criteria to be classified in either type.
[b] Surgery as part of lower-leg injury treatment.
[c] As some patient data were imputed, the total n displays decimals due to imputation,% from known data. Data were missing for the following characteristics: BMI in 100 patients, Smoking in 107 patients, Oral contraceptives use in 45 patients, Cancer in 87 patients, Family history of venous thromboembolism 162 patients.

Table 4
Performance of the TRiP(cast) score in the POT-CAST study.

	AUC (95%CI) in complete cases	AUC (95%CI) in Imputed data		
TRiP(cast) score[a]	0.74 (0.61−0.87)	0.72 (0.60−0.84)		
	Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**
Cutoff 4	100.0	1.9	1.6	100.0
Cutoff 5	95.7	16.6	1.8	99.6
Cutoff 6	85.7	32.2	2.0	99.3
Cutoff 7	76.1	51.2	2.5	99.2
Cutoff 8	64.8	67.9	3.2	99.2
Cutoff 9	53.0	80.0	4.1	99.1
Cutoff 10	45.7	88.8	6.2	99.0
Cutoff 11	31.7	94.4	8.5	98.8

[a] Cut-off represents the value at which the TRiP(cast) score was dichotomized to calculate model performance.
AUC denotes Area under the Curve, PPV denotes positive predictive value, NPV denotes negative predictive value.

0·3332.203*TRiP(cast) score]). The degree of concordance between the observed and predicted risk was estimated by a calibration line with an intercept of 0.0016 and slope of 0.933)
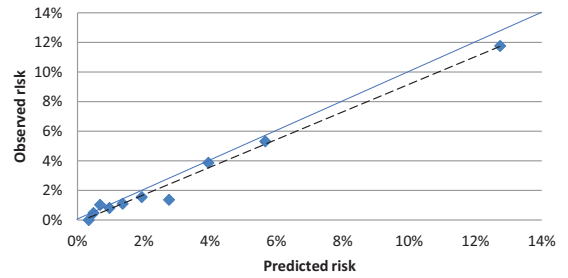
Calibration plot

Fig. 2. Calibration plot in POT-CAST data, showing the observed versus predicted risks for VTE for TRiP(cast) scores 3−12. TRiP(cast) scores ≥12 were summarized in a single dot due to a low number of individuals (3.0%) (observed risk 11.8% and predicted risk 12.8%). For values see Appendix Table A2. Solid Line represents perfect calibration. Dashed line represents calibration line (intercept 0.0016 and slope 0.933). (Axis are truncated at 14% because of the low number of patients with predicted values above 14%.).

(Appendix Table A2). Fig. 2 depicts the calibration plot in which this relationship can be observed.

3.5. Differentiation between a low and high-risk group for symptomatic VTE

The AUC of the TRiP(cast) score in untreated patients in the POT-CAST trial (n = 716) was 0.66 (95%CI 0.49−0.83) whereas for LMWH treated patients (n = 719) the AUC was 0.80 (95%CI 0.67−0.94). 50.7% (n = 728/1435) of all patients had a TRiP(cast) score of <7, and were classified as low-risk patients (mean observed symptomatic VTE risk of 0.8%) whereas 49.3% (n = 707/1435) of patients had a TRiP(cast) score of ≥7, who were classified as high-risk (mean observed symptomatic VTE risk of 2.5%).

Across patients in the low-risk subgroup, 0.4% (1.3/360) of patients treated with LMWH developed symptomatic VTE as compared with 1.1% (4.2/367.8) in the untreated group, for a RR of 0.30 (95%CI 0.03 − 2.60) (absolute numbers represent mean values across 10 imputed datasets, hence, the non-integers). In the high-risk population, 2.4% (8.7/359) of patients treated with LMWH versus 2.5% (8.8/348.2) of untreated patients developed VTE, so here LMWH was non-effective in reducing symptomatic VTE risk (RR 0.96, 95%CI 0.37−2.51).

3.6. Computerized clinical decision support systems

A mobile phone application (TRiP(cast) score © 2018) has been developed (screenshot in Appendix Fig. A2) for IOS (https://apps.apple.com/us/app/trip-cast-score/id1438610930) and Android mobile phone platforms which can be downloaded in the App store of Apple or Android, without costs and is available in three languages; English, Dutch and French. It calculates an individual's absolute predicted risk for VTE (using validation data from this paper) once all patient data have been entered in the application. Decisions on thromboprophylaxis can then be made accordingly.

4. Discussion

In order to facilitate individual VTE risk assessment and guide thromboprophylaxis in patients with lower-limb trauma and cast immobilization, we merged two existing RAMs into the combined TRiP(cast) score. The TRiP(cast) score exhibited good performance in the external validation with an AUC of 0.74 (95%CI 0.61 to 0.87) and the observed and predicted risk were in concordance (calibration slope 0.933). Using <7 points as cut-off, the TRiP(cast) score allows identification of an important subgroup of patients with a low risk of symptomatic VTE (mean absolute risk of 0.8%) who may not require any thromboprophylactic treatment. Contrary, patients with a high-risk of

VTE according to the TRiP(cast) score ($\geq$7 points, mean absolute risk 2.5%) may require intensified or prolonged thromboprophylaxis.

The Leiden-TRiP(cast) and TIP scores were combined for several reasons. First, both scores overlapped on many items which allowed a simple transformation into the final TRiP(cast) score. Second, previous studies have shown that the effect of trauma on VTE risk varies widely according trauma severity and localization [3,16,21]. Whereas the Leiden-TRiP(cast) score lacks such important predictors on trauma severity, this is an important feature of the TIP score. Third, the Leiden-TRiP(cast) score has been validated in two other case-control studies and fewer risk items have to be scored which simplifies use in clinical practice (19 in Leiden-TRiP instead of 30 in the TIP score). Furthermore, the Leiden-TRiP(cast) score does not apply to brace immobilization and contains relatively uncommon items that have been collected using case-control questionnaire data such as pneumonia, or a history of superficial vein thrombosis. By merging the L-TRiP(cast) and TIP score we combined the strengths of both scores to increase the final score's discriminative ability, usability and simplicity. Hence, the combined TRiP(cast) score encompasses 14 items which are easily obtainable in current practice.

The main strength of this paper is that data of the POT-CAST trial were used, which were practically complete and reliable; due to the nature of the POT-CAST trial, trauma severity data have been prospectively collected by a physician and all data on patient characteristics were completed upon inclusion in the trial [6]. Absolute risks for symptomatic VTE were calculated with minimal loss-to follow-up and misclassification, which are common in large registry studies. The strength of the POT-CAST trial (i.e. pragmatic RCT design with non-selected patients and limited exclusion criteria) allowed us to calculate validation statistics in data mimicking clinical practice.

Nevertheless, some limitations have to be mentioned. Although the inclusion criteria of the POT-CAST trial were wide, some patient selection may still have been present. For instance, all patients had plaster cast, i.e. no brace. Patients with a history of VTE were not allowed to participate. However, as their VTE risk is certainly high, it may be reasoned that these patients do not need risk prediction at all, and should receive thromboprophylaxis in most circumstances. Furthermore, despite being the largest trial till date on this topic, few patients (23/1435) developed VTE which limits the accuracy of our validation statistics. The MEGA case-control study was also limited in terms of power. Yet, the predictive performance of the TRiP(cast) score (and previous TIP AND Leiden-TRiP scores) showed consistent results in both the MEGA and POT-CAST datasets indicating no overfitted prediction model. Another limitation might be the use of data imputation which can introduce misclassification (in this case of patient characteristics). However, model performance was good and hardly differed between the imputed and the complete dataset. Lastly, to optimize the TRiP(cast) score performance, 14 variables were maintained which might be considered as relatively many items have to be scored. To anticipate this, we developed a computerized clinical decision support systems (CCDSSs) using a mobile phone application. We believe this can be a helpful tool in clinical practice as entering and summation of the items is greatly facilitated. Furthermore, studies have highlighted that the use of CCDSSs increases the proportion of patients who receive adequate prophylaxis [22,23] and can be efficiently implemented in everyday clinical practice in emergency departments [24].

Current guidelines for thromboprophylaxis and therefore practices vary widely among countries, ranging from the absence of preventive anticoagulation in the US [25] to thromboprophylaxis for all patients for whom plantar support is not possible in France [26]. This variation can be explained by the lack of convincing evidence when these guidelines were written. Some trials showed efficacy of thromboprophylaxis on asymptomatic VTE for patients following lower-limb cast immobilization [27−30]. However, the recent POT-CAST trial failed to demonstrate efficacy of LMWH versus no treatment on the 3-month cumulative incidence of symptomatic VTE with a relative risk of 0·8 (95%CI, 0.3−1.7) [6]. Contrary, a recent Cochrane systematic review and meta-analysis, including these RCTs, showed moderate-quality evidence in favor of thromboprophylaxis for patients with brace or casting [1]. Yet, concerning the methodological issues for many of these trials (e.g. doubtful classification of symptomatic events), inconsistency between the efficacy on asymptomatic vs symptomatic VTE, publication bias towards efficacy and high number needed to treat (250 based on POT-CAST), the quality of evidence was downgraded. The final conclusion of the authors was that future research should give more directives on specific advice for different patients or patients groups, based on patient and trauma characteristics. This goal has now come nearer with the TRiP(cast) score.

To achieve a reduction in VTE risk as well as bleeding, individualized prophylaxis using the TRiP(cast) score might be an important step forward. Ultimately, patients with a high risk may need to receive a higher dosage or duration of thromboprophylaxis or a stronger anticoagulant, while those with a low risk (the majority), can be spared the burden and the costs of an intense treatment.

Individualized therapy will lead to three situations: adequate therapy, under- and over-prescription of anticoagulation. The former is true for all patients with a low- or high-risk who are correctly identified as such. However, as risk assessment is not 100% accurate there is a trade-off which results in under- and over-treatment. Under-prescription arises when high-risk patients are not classified as such, and therefore do not receive thromboprophylaxis (using a cut-off score of $\geq$7, with a corresponding sensitivity of 75%, this occurs in 25% of patients who will eventually develop VTE). Over-prescription occurs when low-risk patients are incorrectly classified as high-risk patients, again, using a cut-off of $\geq$7, 49% of patients receive over-treatment. Opposingly, 51% of patients with a low-risk are correctly withheld from the risks (bleeding) and downsides (costs) of thromboprophylaxis (a cut-off score of 7 was chosen as the absolute VTE risks for patients with a TRiP(cast) score$<$7 was lower than 1.0%). Another approach would be to identify three groups of patients, a low- middle- and high-risk group. In this case, low-risk patients do not require any treatment, middle-risk patients can receive the current dosage and duration of thromboprophylaxis while high-risk patients may need a prolonged and higher dosage of thromboprophylaxis. In this case, high-risk patients could be identified based on a TRiP(cast) score of $\geq$10 which results in an PPV of at least 6.2% (11% of patients).

This strategy is emphasized by the results from our sensitivity analyses in which we found a very limited suggestion for effectiveness for a prophylactic dose of LMWH in low-risk patients (RR 0.30, 95%CI 0.03−2.60) compared with no effectiveness in high-risk patients (RR 0.96 95%CI 0.37−2.51). This finding suggests that a prophylactic dose of LMWH is not sufficient to decrease the thrombosis potential to such an extent that it prevents symptomatic VTE in high-risk individuals.

As we found a different treatment effect across low and high-risk groups, consequently, the predictive value of the TRiP(cast) score was lower in untreated patients than in LMWH treated patients. This might indicate that the TRiP(cast) score particularly identifies high-risk patients despite thromboprophylaxis therapy. However, we have to stress that all these results should be interpreted with care based on the limited the sample size (wide confidence intervals) and hence, low number of patients who developed symptomatic VTE. Overall, the clinical implications of risk stratification and corresponding treatment options will be a subject of debate and is dependent upon prioritizing the classification of low- or high-risk patients, and the

trade-off between under- and over-treatment (i.e. the importance and weight of a false-negative versus false-positive classification).

Despite this study being validated in a large cohort of patients, the ultimate cut-off (in terms of VTE risk) and the corresponding optimal treatment need to be determined in a large management study (including decisions on more intensified treatment regimens). Especially, since the power of our validation study was for low and high-risk patient groups separately. At any rate, it is clear that the current situation needs improvement, as 2.0% of patients develop VTE despite thromboprophylaxis while at the same time a large proportion of this population is likely to be overtreated.

In conclusion, the TRiP(cast) score was developed and validated to predict VTE risk following lower-limb cast or brace immobilization. Thanks to a CCDSS (smartphone application), it can easily be implemented in future research and clinical practice to accurately stratify patients in risk categories and to help in decision making for individualized thromboprophylaxis.

Declaration of Competing Interest

We declare no conflicts of interest.

Acknowledgment

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100270.

Appendix

Tables A1, A2 and Figs. A1, A2.

Table A1
TIP Score, Leiden-TRiP(cast) and TRiP(cast) score items.

	TIP Point value	Leiden-TRiP (cast) point value	TRiP(cast) point value
Trauma			
High-risk trauma: *Fracture of leg bones or proximal tibia fracture, Achilles tendon rupture*	3	–	3
Intermediate risk trauma: *Patellar or one long leg bone fracture; bi or tri-malleolar ankle fracture or ankle dislocation; rear foot dislocation; severe knee sprain (with edema/haemarthrosis); severe ankle sprain (grade 3);*	2	–	2
Low-risk trauma: *Patella, tibiofibular, midfoot or forefoot dislocation; single malleolar ankle fracture; tarsal bone(s) or forefoot fracture; non-severe knee sprain or ankle sprain (grade 1 or 2); important muscle injury.*	1	–	1
Immobilization			
Rigid immobilization including knee	3		3
Complete leg plaster cast		5	
Circular knee plaster cast (ankle free)		2	
Rigid immobilization below the knee	2	4	2
Plaster cast: foot	2	2	1
Semi-rigid without support or foot cast (ankle free)	1	–	1
Patient			
Male	–	1	1
Age ≥ 35 and < 55y	–	2	1
Age ≥55 and <75y	1	3	2
Age ≥ 75y	2	3	3
BMI ≥ 25 and <35 kg/m²	1[a]	1	1
BMI ≥ 35 kg/m²	1	2	2
Personal history of VTE or known major thrombophilia	3	–	4
Family history of VTE (first-degree relative)	2	2	2
Chronic venous insufficiency	1	–	1
Superficial vein thrombosis	–	3	–
Active cancer or myeloproliferative disorder	2	3[b]	3[b]
History of cancer	1	–	–
Recent surgery (≤3 mo.)	2	2	2
Pregnancy or puerperium (≤6 mo.)	2	3	3
Estrogenic hormone therapy (≤2y)	2	4[c]	4[c]
Estrogenic hormone therapy (>2y)	1	4[c]	4[c]
Bedridden within the past 3 mo.	1	2	2
Travel with flight >6 h or history of lower extremity paralysis	1	–	2
Hospital admission within past 3 mo.	–	2	
Pneumonia	–	3	–
Comorbidity	1[d]	1[e]	1[f]

[a] BMI ≥ 30 kg/m².
[b] Cancer within the past 5 years or active cancer.
[c] Current use of oral contraceptives.
[d] Congestive heart failure NYHA > II or chronic respiratory failure or Inflammatory bowel diseases or chronic kidney disease (GFR<50 mL/min).
[e] Rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis.
[f] Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, inflammatory bowel diseases.

Table A2
Observed and predicted risk of the TRiP(cast) score in POT-CAST.

TRiP(cast) score	No event[a]	VTE[b]	Predicted risk[c] (%)	Observed risk (%)
1	0	0	0.18	0.00
2	0	0	0.25	0.00
3	27.2	0	0.35	0.00
4	207.8	1	0.49	0.48
5	220	2.3	0.69	1.03
6	267.3	2.2	0.97	0.82
7	235.9	2.6	1.37	1.09
8	172	2.7	1.95	1.54
9	123.7	1.7	2.77	1.36
10	79.7	3.2	3.95	3.85
11	40.9	2.3	5.67	5.30
12	19.1	4	8.16	17.37
13	9.7	0	11.76	0.00
14	5.3	1	16.95	15.95
15	1.2	0	24.30	0.00
16	0.1	0	34.39	0.00
17	2.1	0	47.59	0.00
Total	1412	23		

[a] Number of patients without a VTE.
[b] Number of patients with a VTE, rounded in decimals because of imputation.
[c] Logistic regression formula $y = a + bx$, $y = -6.677015 + 0.3332203x$, predicted risk calculated by $\exp(-6.677015 + 0.3332203*\text{TRiP(cast) score})/1+ \exp(-6.677015 + 0.3332203*\text{TRiP(cast) score})$.
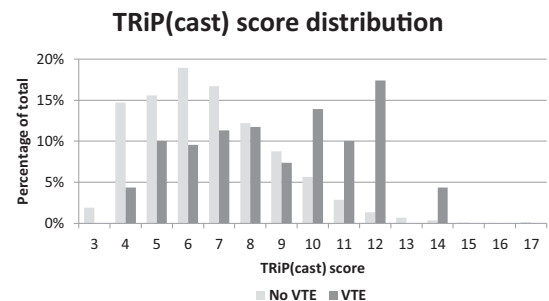

TRiP(cast) score distribution

Fig. A1. TRiP(cast) score distribution for all patients in the POT-CAST trial.
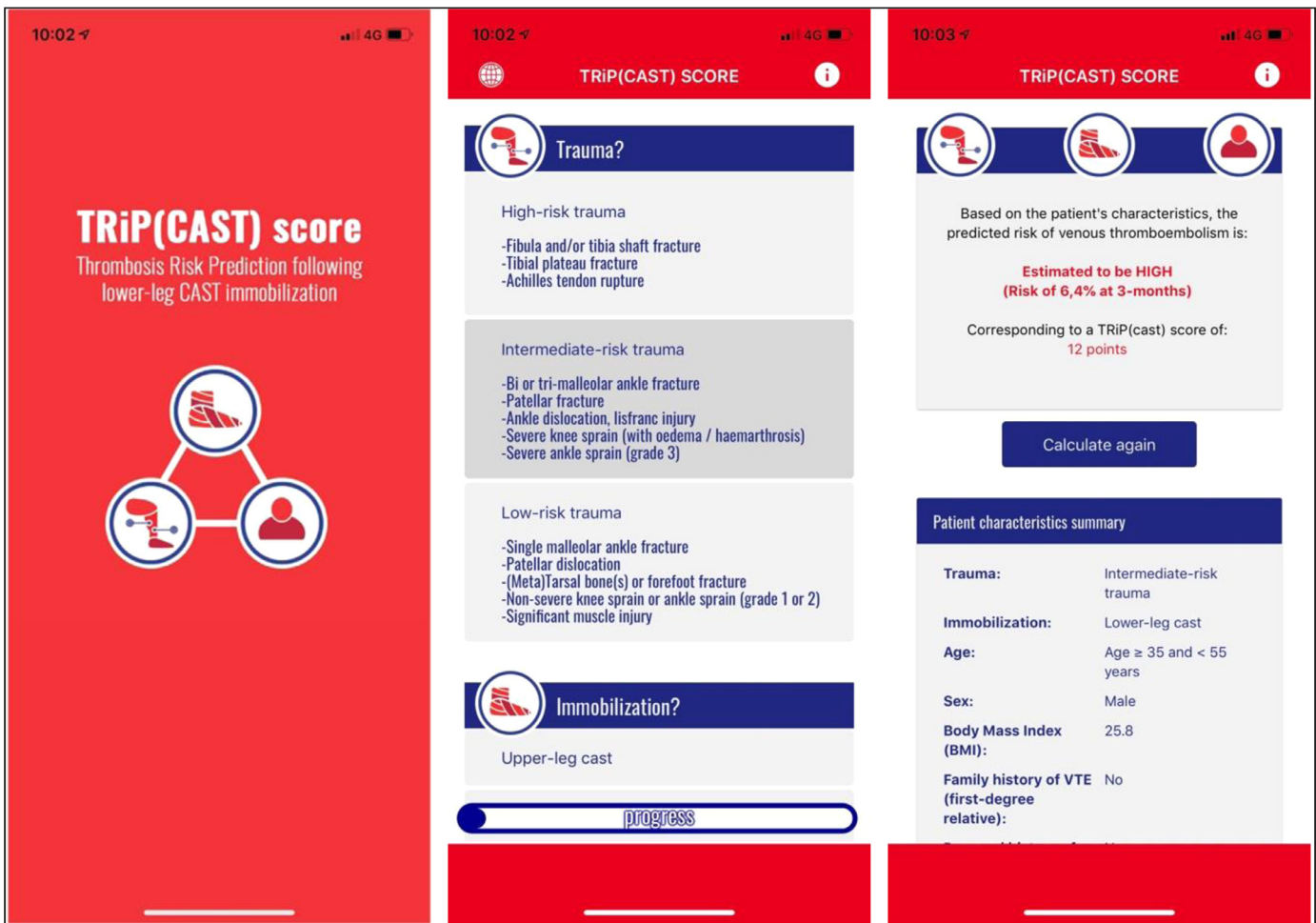
Fig. A2. Screenshots of the IOS mobile phone application for the TRiP(cast) score.

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