Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy

Németh, B.

10

Predicting venous thromboembolism risk after immobilization of the lower-limb for trauma: update and validation of a clinical risk assessment model, the TRiP(cast) score

*B.Németh, *D. Douillet, S. le Cessie, A. Penaloza,
T. Moumneh, PM. Roy, S.C. Cannegieter
*Authors contributed equally

The Lancet - EClinicalMedicine. 2020 Feb 4;20:100270.

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 aetiology 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 to 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.

Funding source ZonMW VIMP grant:17110200011.

BACKGROUND

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].

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".

Goals of this investigation

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.

METHODS

Study methods

Figure 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, Figure 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, Figure 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, Figure 1*) [6].

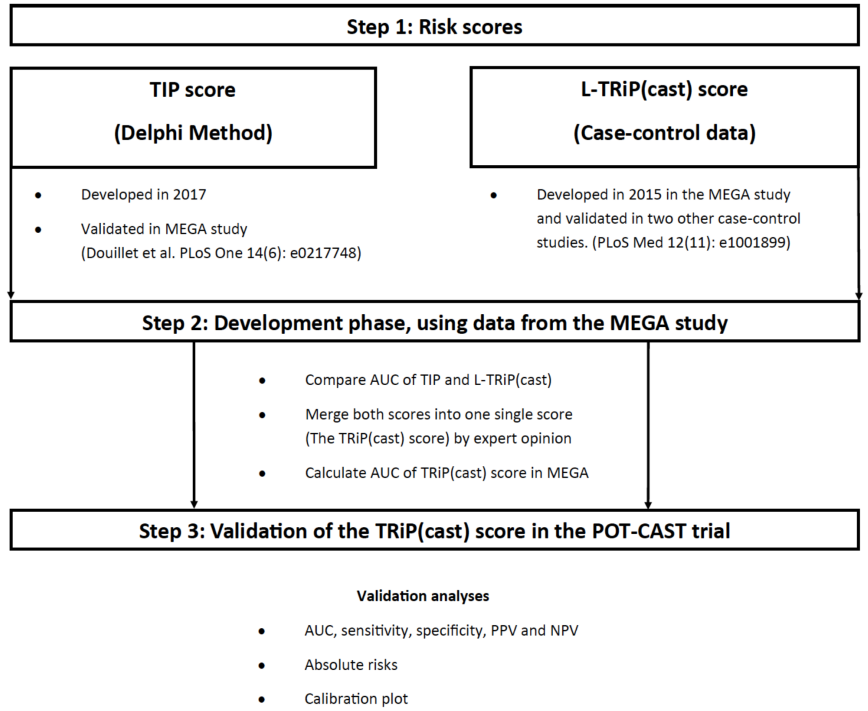


Figure 1: Flowchart of the TRiP(cast) score development and validation process.

Formation of the final TRiP(cast) score

Appendix Table 1 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.

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.

Study Design

The 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 to 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 dialling 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), (orthopaedic) surgery, current use of (any) medication, and comorbidity in the past year before VTE.

The 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 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 fulfil 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.

Statistical analysis

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].

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 ± 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.

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.

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 and Android mobile platforms.

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.

RESULTS

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 30kg/m² 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 <35kg/m²). 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.

Table 1: TRiP(cast) score*.

Trauma †	Points
High-risk trauma Fibula and/or tibia shaft fracture Tibial plateau fracture Achilles tendon rupture	3
Intermediate risk trauma Bi or tri-malleolar ankle fracture Patellar fracture Ankle dislocation, Lisfranc injury Severe knee sprain (with oedema / haemarthrosis) Severe ankle sprain (grade 3)	2
Low-risk trauma 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	1

Table 1: Continued.

	Points
Immobilization ‡	
Upper-leg cast	3
Lower-leg cast	2
Foot cast (ankle free) or any semi-rigid without plantar support	1
Patient characteristics §	
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 ≥35kg/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 within the past 5 years or active cancer	3
Pregnancy or puerperium	3
Immobilization (other) ||	
Hospital admission, bedridden or flight > 6 hours within 3 months	2
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

* Thrombosis Risk Prediction in patients with cast immobilization score
TRiP(cast) score is the sum of the Trauma, Immobilization and Patient components
† Trauma: Choose one, (the most severe trauma)
‡ Immobilization: Choose one
§ Patient: multiple points can be scored
|| Other immobility next to cast immobilization

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*).

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

	AUC*	**95% CI**	
L-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

*AUC denotes Area Under the Curve, CI denotes Confidence Interval

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/m². 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).

TRiP(cast) score performance

The distribution of the TRiP(cast) score among patients with or without VTE is displayed in *Appendix figure 1*. The TRiP(cast) score performed well with an AUC of 0.74 (95%CI 0.61 to 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%.

Table 3: POT-CAST trial – validation cohort characteristics.

	Total n=1435
Trauma	
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 *	11 (0.8)
Surgery, n (%) †	170 (11.8)
Patient characteristics ‡	
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)

Table 3: Continued.

	Total n=1435
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
* Fractures not meeting criteria to be classified in either type.
† Surgery as part of lower-leg injury treatment
‡ As some patient data were imputed, the total n displays decimals due to imputation. 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 316 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	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%

* 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
† Based on a VTE prevalence of 1.6%

The predicted risk (absolute VTE risk) was calculated by exp(6.677015 + 0.3332203*TRiP(cast) score)/(1+ exp[6.677015 + 0.3332203*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) (*Appendix Table 2*). *Figure 2* depicts the calibration plot in which this relationship can be observed.

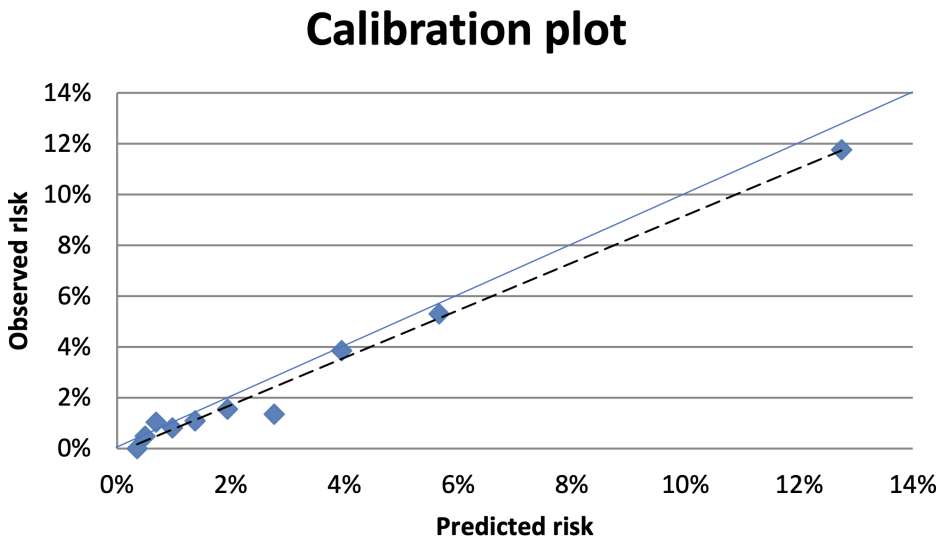


Figure 2: Calibration plot, showing the observed versus predicted risks for VTE for TRiP(cast) scores 3-12. TRiP(cast) scores ≥12 were summarized in a single dot due to a low number of events (3.0%) (observed risk 11.8% and predicted risk 12.8%). For values see *Appendix Table 2*.

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

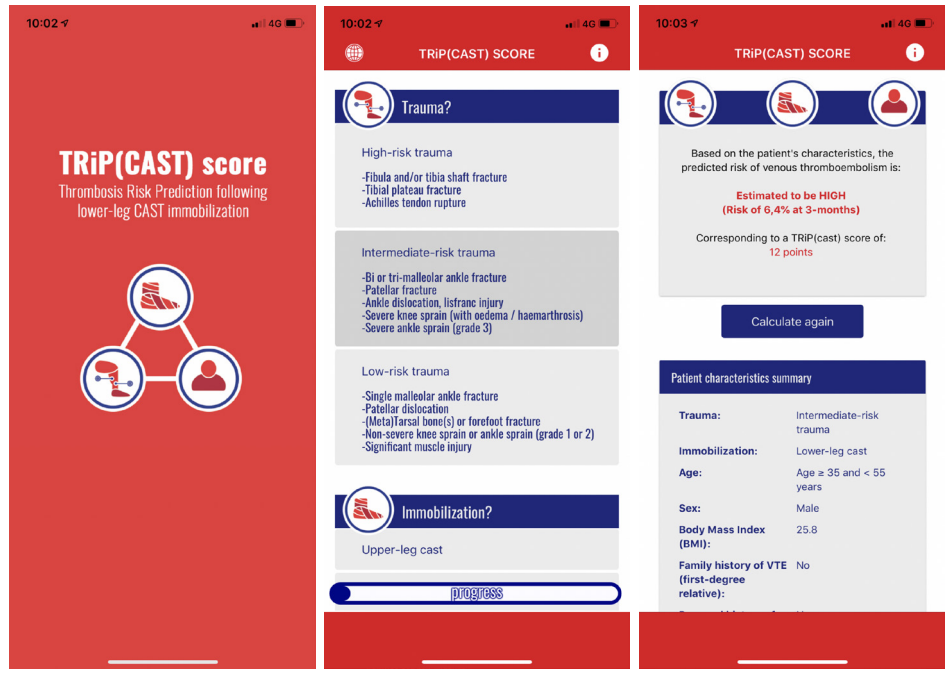
The AUC of the TRiP(cast) score in untreated patients in the POT-CAST trial (n=716) was 0.66 (95%CI 0.49-0.83) whereas for LMWH treated patients (n=719) the AUC was 0.80 (95%CI 0.67-0.94). 50.7% (n=728/1435) of all patients had a TRiP(cast) score of <7, and were classified as low-risk patients (mean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

Computerized clinical decision support systems

A mobile phone application (TRiP(cast) score © 2018) has been developed (screenshot in *Appendix Figure 2*) for IOS 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.



Appendix Figure 2: Screenshots of the TRiP(cast) score © 2018 mobile phone application.

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 (≥ 7 points, mean absolute risk 2.5%) may require intensified or prolonged thromboprophylaxis.

Merging risk scores

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.

Strengths and limitations of the study

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].

From a population-based approach to individualized therapy

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 to 1.7) [6]. Contrary, a recent Cochrane systematic review and meta-analysis, including these RCTs, showed moderate-quality evidence in favour 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.

Clinical implications

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 ≥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 ≥7, 49% of patients receive overtreatment. 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 ≥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.

REFERENCE LIST

1. 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. Database Syst Rev. 2017 Aug 6;8(8):CD006681.
2. 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 Oct 8;(4):CD006681.
3. van Adrichem RA, Debeij J, Nelissen RGHH, Schipper IB, Rosendaal FR, Cannegieter SC. Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study. J Thromb Haemost. 2014 Sep;12(9):1461–9.
4. Ettema HB, Kollen BJ, Verheyen CCPM, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. J Thromb Haemost. 2008 Jul;6(7):1093–8.
5. Hickey BA, Watson U, Cleves A, Alikhan R, Pugh N, Nokes L, et al. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. Foot and Ankle Surgery. 2018 Feb;24(1):19–27.
6. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. New England Journal of Medicine. 2017 Feb 9;376(6):515–25.
7. Lambers K, Ootes D, Ring D. Incidence of patients with lower extremity injuries presenting to US emergency departments by anatomic region, disease category, and age. Clin Orthop Relat Res. 2012 Jan;470(1):284–90.
8. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15 000 adults: The influence of age and gender. The Journal of Bone and Joint Surgery. 1998 Mar 1;80(2):243–8.
9. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. Journal of Thrombosis and Haemostasis. 2007 Apr;5(4):692–9.
10. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. Journal of Thrombosis and Haemostasis. 2014 Oct;12(10):1580–90.
11. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. Journal of Thrombosis and Thrombolysis. 2009 Nov;28(4):465–76.
12. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010 Nov;8(11):2450–7.
13. Caprini JA. Individual Risk Assessment Is the Best Strategy for Thromboembolic Prophylaxis. Disease-a-Month. 2010 Oct;56(10):552–9.
14. Németh B, Adrichem RA van, Hylckama Vlieg A van, 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. Sattar N, editor. PLOS Medicine. 2015 Nov 10;12(11):e1001899.
15. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005 Feb 9;293(6):715–22.

16. Bezemer ID, Doggen CJM, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. 2007 Mar 12;167(5):497–501.
17. Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). PLoS Med. 2006 Aug;3(8):e307.
18. van Stralen KJ. Minor Injuries as a Risk Factor for Venous Thrombosis. Archives of Internal Medicine. 2008 Jan 14;168(1):21.
19. Riou B, Rothmann C, Lecoules N, Bouvat E, Bosson J-L, Ravaud P, et al. Incidence and risk factors for venous thromboembolism in patients with nonsurgical isolated lower limb injuries. Am J Emerg Med. 2007 Jun;25(5):502–8.
20. Borab ZM, Lanni MA, Tecce MG, Pannucci CJ, Fischer JP. Use of Computerized Clinical Decision Support Systems to Prevent Venous Thromboembolism in Surgical Patients: A Systematic Review and Meta-analysis. JAMA Surgery. 2017 Jul 1;152(7):638.
21. Galanter WL, Thambi M, Rosencranz H, Shah B, Falck S, Lin F-J, et al. Effects of clinical decision support on venous thromboembolism risk assessment, prophylaxis, and prevention at a university teaching hospital. American Journal of Health-System Pharmacy. 2010 Aug 1;67(15):1265–73.
22. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e278S-e325S.
23. Samama C-M, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, et al. [French Society of Anaesthesia and Intensive Care. Guidelines on perioperative venous thromboembolism prophylaxis. Update 2011. Short text]. Ann Fr Anesth Reanim. 2011 Dec;30(12):947–51.
24. Kock H-J, Schmit-Neuerburg KP, Hanke J, Rudofsky G. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. The Lancet. 1995 Aug;346(8973):459–61.
25. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002 Sep 5;347(10):726–30.
26. J Lapidus L, Ponzer S, Elvin A, Levander C, Lärfars G, Rosfors S, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: A randomized placebo-controlled, double-blind study. Acta Orthopaedica. 2007 Jan;78(4):528–35.
27. Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, et al. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA): A phase II, multicentre, double-blind, placebo-controlled randomised study. Thrombosis and Haemostasis. 2016 Mar;116(08):349–55.
28. Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ, et al. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017 Apr;48(4):936–40.