Targeted prophylactic anticoagulation based on the TRiP(cast) score in patients with lower limb immobilisation: a multicentre, stepped wedge, randomised implementation trial

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Summary

Background Prophylactic anticoagulation in emergency department patients with lower limb trauma requiring immobilisation is controversial. The Thrombosis Risk Prediction for Patients with Cast Immobilisation—TRiP(cast)—score could identify a large subgroup of patients at low risk of venous thromboembolism for whom prophylactic anticoagulation can be safely withheld. We aimed to prospectively assess the safety of withholding anticoagulation for patients with lower limb trauma at low risk of venous thromboembolism, defined by a TRiP(cast) score of less than 7.

Methods CASTING was a stepped-wedge, multicentre, cluster-randomised trial with blinded outcome assessment. 15 emergency departments in France and Belgium were selected and randomly assigned staggered start dates for switching from the control phase (ie, anticoagulation prescription according to the physician's usual practice) to the intervention phase (ie, targeted anticoagulation according to TRiP(cast) score: no prescription if score <7 and anticoagulation if score was ≥7). Patients were included if they presented to a participating emergency department with lower limb trauma requiring immobilisation for at least 7 days and were aged 18 years or older. The primary outcome was the 3-month cumulative rate of symptomatic venous thromboembolism during the intervention phase in patients with a TRiP(cast) score of less than 7. The targeted strategy was considered safe if this rate was less than 1% with an upper 95% CI of less than 2%. The primary analysis was performed in the intention-to-treat population. This study is registered at ClinicalTrials.gov (NCT04064489).

Findings Between June 16, 2020, and Sept 15, 2021, 15 clusters and 2120 patients were included. Of the 1505 patients analysed in the intervention phase, 1159 (77·0%) had a TRiP(cast) score of less than 7 and did not receive anticoagulant treatment. The symptomatic venous thromboembolism rate was 0·7% (95% CI 0·3–1·4, n=8/1159). There was no difference between the control and the intervention phases in the cumulative rate of symptomatic venous thromboembolism or in bleeding rates.

Interpretation Patients with a TRiP(cast) score of less than 7 who are not receiving anticoagulation have a very low risk of venous thromboembolism. A large proportion of patients with lower limb trauma and immobilisation could safely avoid thromboprophylaxis.

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Introduction

Patients with lower limb trauma requiring immobilisation are at increased risk of symptomatic venous thromboembolism, with an estimated 3-month cumulative venous thromboembolism incidence of 2·0% (95% CI 1·3–2·7).[1] Anticoagulant treatment, mainly low-molecular-weight heparin (LMWH) and fondaparinux, reduces the rate of venous thromboembolism,[2,3] but there is still debate as to whether this treatment should be routinely prescribed in all such patients. Indeed, the thrombotic risk varies considerably between patients (eg, from young patients with knee sprains to diaphyseal fractures in older people). The POT-CAST study[4] did not show the efficacy of LMWH to prevent venous thromboembolism events in an unselected population of patients with a lower limb trauma. There is an emerging consensus about the necessity of identifying patients at low risk of venous thromboembolism, to restrict anticoagulant use to patients deemed to be at high risk.[2,4–7] In Europe, current guidelines nevertheless advocate use of anticoagulants for all patients until weight bearing is resumed.[8,9] Owing to the high prevalence of lower limb trauma, the inconvenience of daily anticoagulant

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Research in context

Evidence before this study

To prevent venous thromboembolic events in patients with immobilised lower limb due to trauma, prophylactic treatment with low-molecular-weight heparin or fondaparinux has been shown to be effective. However, this population is highly heterogeneous, leading to important variations in venous thromboembolism risk among patients and variations in current recommendations among countries. Many authors consider that a targeted strategy based on a risk stratification model must be defined. We searched the literature to identify evidence of targeted thromboprophylaxis in patients with a lower limb trauma requiring immobilisation. We searched PubMed using the terms ("Risk model*" or "prognostic model" or "prediction model" or "risk assessment model" or "prediction score*" or "algorithm*" or "prediction rule" or "decision rule*" or "risk score") AND ("thromboprophyla*" or "thrombus" or "thrombotic" or "thrombolic*" or "thromboemboli*" or "thrombos*" or "embol*") AND ("immobili*" or "brac*" or "cast*" or "plaster") AND ("leg" or "tibia*" or "fibula" or "foot" or "Achille" or "tendon*") AND ("fractur*" or "sprain" or "trauma*") for publications (including abstracts and posters) in any language published between Jan 1, 2000, and June 1, 2023. Publications were excluded primarily if they involved children or elective surgery. We found five risk assessment models. The Plymouth rule was established by expert consensus but has not yet been validated. The Leiden Thrombosis Risk Prediction for Patients with Cast Immobilisation—TRiP(cast)—score was developed from a case–control database and validated retrospectively. The Trauma, Immobilisation and Patient Characteristics (TIP) score is an expert consensus model developed via a Delphi method and was validated retrospectively. The TRiP(cast) score was established by combination of the Leiden TRiP(cast) score and the TIP score and was retrospectively validated. The Aberdeen rule is an expert consensus model that was prospectively evaluated and compared with other prediction models. We concluded that the TRiP(cast) score was the most promising model to accurately predict venous thromboembolism risk and target thromboprophylaxis. The aim of the present trial was to prospectively evaluate the safety and efficacy of targeting anticoagulation in patients with lower limb trauma according to the TRiP(cast) score.

Added value of this study

In this stepped-wedge, cluster-randomised trial, the 3-month rate of symptomatic venous thromboembolic events in patients at low risk—ie, with a TRiP(cast) score of less than 7—receiving no prophylactic anticoagulant was lower than the prespecified safety threshold. As compared with current practice in France and Belgium (ie, the control phase), the implementation of the targeted strategy halved the anticoagulation prescription rate without significant increase in the overall 3-month venous thromboembolism rate. To our knowledge, this study is the first implementation trial to assess a venous thromboembolism risk assessment strategy in traumatology to target anticoagulation.

Implications of all the available evidence

This trial supports, with a high quality of evidence, the feasibility and the favourable effects of a targeted strategy to individualise thromboprophylaxis prescription in lower limb trauma patients. Based on the TRiP(cast) score, a large subgroup of patients are at low risk of venous thromboembolism and do not require thromboprophylaxis in contrast to a small subgroup of patients with high venous thromboembolism risk who warrant prophylactic anticoagulation. The TRiP(cast) score can safely help physicians in decision making and avoid anticoagulation treatment with daily subcutaneous injection for almost three-quarters of patients with lower limb immobilisation.

injections for the patient, and the substantial effect of venous thromboembolism on morbidity, mortality, and resource expenditure, targeted prophylactic anticoagulation could have a major impact on public health burden.

The Thrombosis Risk Prediction for Patients with Cast Immobilisation—TRiP(cast)—score aims to predict the absolute risk of venous thromboembolism within 3 months after lower limb trauma requiring immobilisation.[10] This score is based on 14 criteria including trauma, immobilisation, and patient characteristics (panel) and was designed to help physicians to decide whether to prescribe a prophylactic anticoagulant. The TRiP(cast) score has been retrospectively validated in both a trial population (POT-CAST trial) and a cohort study.[10,11] Patients with a TRiP(cast) score less than 7 have a venous thromboembolism risk of less than 1%.[10] We hypothesised that, for patients with isolated lower limb trauma requiring immobilisation, the TRiP(cast) score can be used to define a large subgroup of patients who do not require preventive anticoagulation.

The aim of this study was to prospectively assess the safety of withholding anticoagulation for patients with lower limb trauma at low risk of venous thromboembolism, defined by a TRiP(cast) score of less than 7.

See Online for appendix

Methods

Study design

This multicentre, stepped-wedge, cluster-randomised clinical trial was done in 15 emergency departments in France and Belgium (of various sizes and across various locations; appendix p 2). A cluster, stepped-wedge design was chosen because the aim was to compare implementation of the TRiP(cast) score and current practices,[12] which varies from one physician to another

and one centre to another. This design facilitates recruitment in participating emergency departments and reduces the risk of contamination between groups.[12] The trial protocol is available in the appendix (pp 16–117), and has been previously published.[13] The trial was approved by ethics committees of Angers (ID-RCB:2019-A01829) for French centres and of Brussels (No B403201941338) for Belgian centres and was reported in accordance with the CONSORT statement extended to stepped-wedge, cluster-randomised trials.[12,14]

Clusters and patients

Clusters were eligible if the emergency department had already participated in prospective multicentre research or if they had research staff and a significant recruitment capacity, assessed by the number of patients presenting to the emergency department with lower limb trauma (with no prespecified cutoff). The emergency department medical staff had to confirm their willingness to participate in the study. There were no predefined centre exclusion criteria once the study had started. Only centres that were unable to continue their participation in the study were excluded. If centres of similar size and location did not include enough patients, they were grouped together.

Patients were eligible for the trial if they were aged 18 years or older and presented to an emergency department with lower limb trauma requiring immobilisation for an anticipated duration of at least 7 days. Immobilisation comprised the use of rigid fibreglass, plaster casts, or rigid devices, such as rigid knee or ankle splints with or without weight bearing. Patients were excluded if they were receiving anticoagulation treatment at the time of inclusion or if hospitalisation for more than 2 days was planned at this time. Patients with no national health insurance coverage, or who were incarcerated or under guardianship, were also excluded. All patients included provided their written informed consent to participate in the study before discharge from the emergency departments.

Randomisation and masking

After an initial control phase of 3 weeks in all 15 centres, one of the emergency departments was switched to the intervention phase about every 2 weeks according to a random permutation sequence generated with R (version 4.0.2) with a random seed set by an independent statistician. Before the beginning of the study and during the control phase, health-care workers were unaware of the nature of the intervention and use of the TRiP(cast) score was not recommended. Once all centres had switched, the interventional phase was prolonged until inclusion of the target number of patients was complete (appendix p 11). All possible primary and secondary outcome events were assessed by a masked independent outcome adjudication committee. For this purpose, the files of patients with suspected venous thromboembolism or bleeding were collected by a research assistant and all

Panel: **TRiP(cast) score***

Trauma†

High-risk trauma (points=3)
Fibula or tibia shaft fracture
Tibial plateau fracture
Achilles tendon rupture
Intermediate-risk trauma (points=2)
Bimalleolar or trimalleolar ankle fracture
Patellar fracture
Ankle dislocation, Lisfranc injury
Severe knee sprain (with oedema or haemarthrosis)
Severe ankle sprain (grade 3)
Low-risk trauma (points=1)
Single malleolar ankle fracture
Patellar dislocation
Tarsal or metatarsal bones or forefoot fracture
Non-severe knee sprain or ankle sprain (grade 1 or 2)
Significant muscle injury

Immobilisation‡

Upper-leg cast (points=3)
Lower-leg cast (points=2)
Foot cast (ankle free) or any semi-rigid cast without plantar support (points=1)
Other cast or bracing with plantar support (points=0)

Patient characteristics§

Age <35 years (points=0)
Age ≥35 and <55 years (points=1)
Age ≥55 and <75 years (points=2)
Age ≥75 years (points=3)
Male sex (points=1)
BMI ≥25 kg/m^2 and <35 kg/m^2 (points=1)
BMI ≥35 kg/m^2 (points=2)
Family history of venous thromboembolism—first-degree relative (points=2)
Personal history of venous thromboembolism or known major thrombophilia (points=4)
Current use of oral contraceptives or oestrogenic hormone therapy (points=4)
Cancer diagnosis within the past 5 years (points=3)
Pregnancy or puerperium (points=3)
Immobilisation (other than cast-related) within the past 3 months—ie, hospital admission, bedridden or flight >6 h, or lower limb paralysis (points=2)
Surgery within the past 3 months (points=2)
Comorbidity—ie, heart failure, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, or inflammatory bowel disease (points=1)
Chronic venous insufficiency—ie, varicose veins (points=1)

*Thrombosis Risk Prediction for Patients with Cast Immobilisation score. The TRiP(cast) score is the sum of the points scored for the trauma, immobilisation, and patient characteristic components. †Choose one (the most severe trauma). ‡Choose one. §Multiple points can be scored.

the elements related to the centre, the study phase (control or intervention), and eventual calculation of the TRiP(cast) score were concealed before submission to the adjudication committee.

Procedures

In both study phases, patients admitted to participating emergency departments for lower limb trauma were assessed continuously for eligibility. Enrolment was performed by the senior emergency physician-in-charge. During the control phase, physicians were completely autonomous in their decision to prescribe or not to prescribe an anticoagulant (mainly the LMWH enoxaparin 40 mg once daily or fondaparinux 2·5 mg once daily, depending on local practice). Prophylactic anticoagulation was prescribed by the emergency physicians, most often for the entire duration of lower limb immobilisation. The exact duration of anticoagulation was left to the discretion of the physician in charge of the patient. After indicating whether anticoagulation had been prescribed, the investigator recorded the patient's characteristics, including their risk factors for thromboembolism, the type of trauma, the type of immobilisation, and the anticipated length of immobilisation. The sex variable was collected according to sex at birth.

During the intervention phase, the TRiP(cast) score was used to target prophylactic anticoagulation with an online application. The physicians were advised to prescribe an anticoagulant treatment (LMWHs or fondaparinux, depending on local practice) for patients with a TRiP(cast) score of 7 or higher, and to withhold prophylactic anticoagulation in patients with a score less than 7. The treatment was initiated in the emergency department or on the first day after discharge. The treatment was then dispensed at the pharmacy. In both phases (control and intervention), enrolled patients received a study participation card, including emergency telephone numbers and the telephone number of the local principal investigator of the trial. Patients also received a brochure describing the signs and symptoms suggestive of venous thromboembolism or bleeding and were advised to seek medical care in the event of their occurrence. Patients were contacted by telephone at 1 month and 3 months to assess whether they had undergone any assessment for suspected venous thromboembolism, bleeding, and whether they had adhered to the assigned regimen. If any patient did not respond, their general practitioner was contacted to determine whether any trial outcome event or death had occurred. If this approach was also unsuccessful, the hospital administrative records were consulted and the administrative records at the patient's place of birth were checked for evidence of death.

Outcomes

The primary objective was to assess the safety of the strategy of withholding anticoagulation in patients with lower limb immobilisation and a TRiP(cast) score less than 7 during the intervention phase. The primary outcome was the rate of symptomatic venous thromboembolism (ie, the cumulative incidence of symptomatic deep vein thrombosis or pulmonary embolism, fatal pulmonary embolism, and unexplained sudden death) within 3 months after inclusion in this low-risk population.[15,16] This targeting strategy was considered safe if the venous thromboembolism rate was less than 1% with an upper 95% CI of less than 2% among patients with a TRIP(cast) score of less than 7 in the intervention group (ie, the group not receiving prophylactic anticoagulants).[4] Secondary endpoints were the rate of patients receiving an anticoagulant prescription, the rate of symptomatic venous thromboembolism at 3 months after inclusion, the cumulative incidences of major bleeding and clinically relevant non-major bleeding (according to the International Society on Thrombosis and Hemostasis criteria[17] in both the control and intervention phases), and the differences in these rates between the two phases. The occurrence of heparin-induced thrombocytopenia was assessed in both phases. The performance of the TRiP(cast) score was described in terms of the area under the curve and the corresponding 95% CI, as well as the sensitivity, specificity, and positive and negative predictive values. Satisfaction with the application used as a case report form and calculator of the TRiP(cast) score was assessed on a 5-point Likert scale. All possible primary and secondary outcome events were assessed by a masked independent outcome adjudication committee. The definitions of the outcomes and the list of the members of the committee are provided in the appendix (pp 119–135).

Statistical analysis

The sample size was calculated with respect to a prespecified limit. Assuming a symptomatic venous thromboembolism rate of 1% in patients with a TRiP(cast) score less than 7 and therefore not receiving anticoagulant treatment, 858 patients were required in this subgroup to achieve an upper bound 95% CI of 2% or less (below the rate observed in the treated group of the POT-CAST 2·5% study).[4,10] Additionally, assuming that this subgroup of patients at low risk would represent 60% or more of the included population and that the rate of patients lost to follow-up or with unanalysable data would reach 5%, the number of patients to be included in the intervention phase was set at 1500.[4,18] The number of patients to be included in the control phase was established on the basis of the anticoagulant prescription rate. Assuming a 15% decrease in the rate of prescription of prophylactic anticoagulation during the intervention phase compared with the control phase, the participation of 15 centres, and an intraclass correlation coefficient (centre effect) at 0·1, the inclusion of 540 patients was deemed necessary to show a significant difference between the two phases with a two-sided α level of 5% and a power of 80%.[19,20] Taking into account the possibility of patients lost to follow-up or

not analysable, the number of patients to be included in the control phase was set at 600. The total number of research participants was therefore set at 2100 patients.

The statistical analysis plan is provided in the appendix (pp 97–118).

To assess the safety of the decision to withhold anticoagulation according to the TRiP(cast) score, the primary analysis was performed in the intention-to-treat population—ie, all randomly assigned patients. The initial analysis was planned to be in the per-protocol population. The statistical analysis plan was modified to allow for analysis in the intention-to-treat and per-protocol populations. A sensitivity analysis was performed in the per-protocol population (ie, excluding patients with major protocol deviations). Major protocol deviations were non-respect of the targeted strategy in the intervention group (ie, anticoagulant prescription for patients with a TRiP(cast) score <7) or curative anticoagulation for a reason other than venous thromboembolism during the 3 months following inclusion. Baseline characteristics were reported as numbers and percentages for categorical variables and either mean and SD or median and IQR for continuous variables, depending on their distribution. To avoid multiple testing, a hierarchical management of objectives was implemented (appendix pp 97–118). We calculated the 3-month rate of symptomatic venous thromboembolism and its 95% CI with the Clopper–Pearson approach. The anticoagulant prescription rate and venous thromboembolism incidence in the overall population were compared between the two phases in the intention-to-treat population with a logistic mixed model, with the random variable phase as fixed effect and a random intercept on the centre. We then reported risk-difference estimates and 95% CIs for all other secondary outcomes but did not do formal hypothesis testing. To determine a 95% CI, a Bonferroni correction was done allowing control of the family-wise error rate at 5%. In the case of rare events (<2%) or when the model did not converge or the variance-covariance matrix was singular, an exact estimation of the confidence interval by the Clopper–Pearson method was preferred. The performance of the TRiP(cast) score was assessed with the area under the receiver operating characteristic curve with a discriminant value set at a threshold of 7 (for determination of sensitivity, specificity, and negative and positive predictive values).

All analyses were carried out with R (version 4.0.2). There was no data monitoring committee for this study. This study is registered at ClinicalTrials.gov (NCT04064489).

Role of the funding source

The funder of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. Both DD and P-MR had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

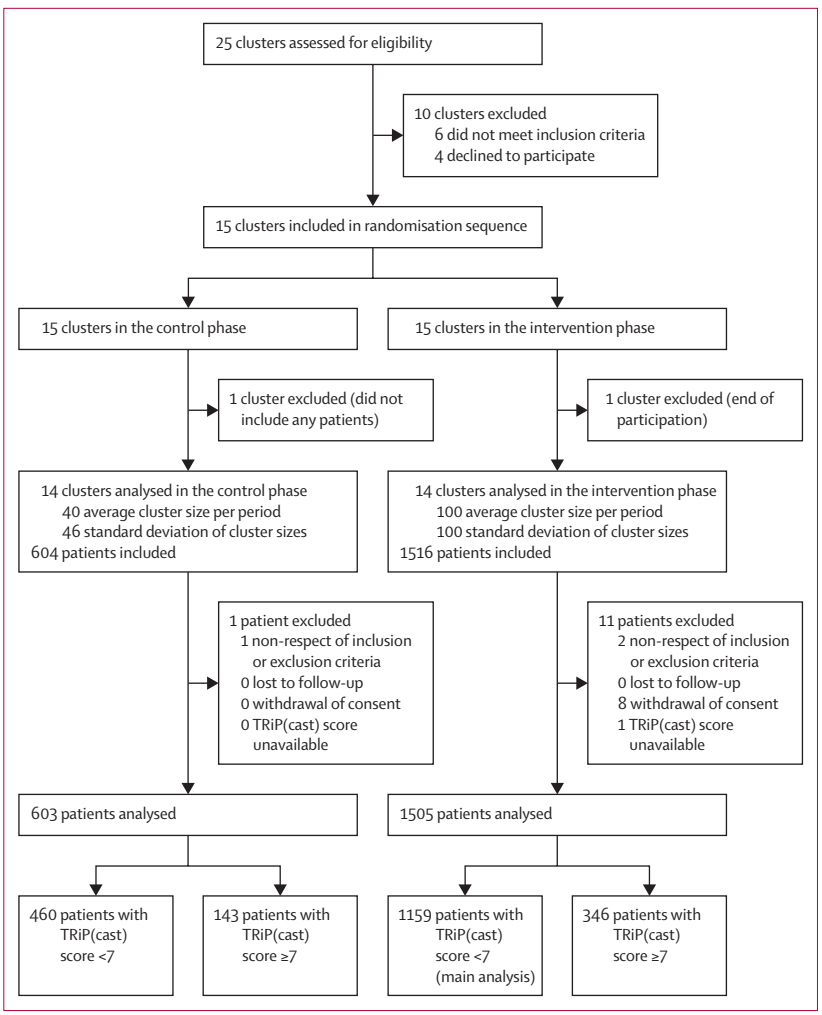

Figure: **Flowchart showing the number of clusters and patients in both phases**

Results

The study took place from June 16, 2020, to Sept 15, 2021. 15 clusters were included in the control phase. 15 clusters were included in the intervention phase, but one centre was unable to continue its participation and was secondarily excluded after the inclusion of no patients in the control phase (figure, appendix pp 7, 11). A total of 2120 patients were included in the 15 emergency departments participating in the trial, of whom 12 (0·6%) were excluded, leading to a total of 2108 patients in the intention-to-treat population: 603 patients in the control phase and 1505 in the intervention phase (figure). Patients' characteristics were similar between the two phases (table 1); in total 1005 (47·7%) were female and the median age was 35 (IQR 24–49) years. The most frequent injury was ankle sprain (1040 patients, 49·3%). The median length of immobilisation was 21 (IQR 10–34) days. The TRiP(cast) score distribution is presented in the appendix (p 3).

Among patients included in the intervention phase, 1159 (77·0%) had a TRiP(cast) score less than 7. In these

	Primary analysis: intervention phase—patients with TRiP(cast) score <7 (n=1159)	Secondary analyses: intervention phase—intention-to-treat patients (n=1505)	Secondary analyses: control phase—intention-to-treat patients (n=603)
Age (years)*	31 (23–44)	35 (25–52)	35 (24–49)
<35	668 (57·6%)	748 (49·7%)	295 (48·9%)
≥35 to <55	375 (32·4%)	508 (33·8%)	182 (30·2%)
≥55 to <75	111 (9·6%)	226 (15·0%)	109 (18·1%)
≥75	5 (0·4%)	23 (1·5%)	17 (2·8%)
Sex			
Female	501 (43·2%)	716 (47·6%)	289 (47·9%)
Male	658 (56·8%)	789 (52·4%)	314 (52·1%)
BMI (kg/m²)*†	23·9 (21·7–26·8)	24·3 (21·9–27·4)	24·7 (22·1–28·5)
<25	717 (61·9%)	850 (56·5%)	325 (53·9%)
≥25 to <35	410 (35·4%)	590 (39·2%)	252 (41·8%)
≥35	31 (2·7%)	63 (4·2%)	25 (4·1%)
Comorbidities			
Personal history of venous thromboembolism	2 (0·2%)	35 (2·3%)	14 (2·3%)
History of first-degree venous thromboembolism	42 (3·6%)	115 (7·6%)	39 (6·5%)
Oral contraceptive use or oestrogenic hormone therapy	49 (4·2%)	146 (9·7%)	68 (11·3%)
Active cancer within the past 5 years	2 (0·2%)	15 (1·0%)	6 (1·0%)
Postpartum period‡	0 (0·0%)	5 (0·3%)	1 (0·2%)
Immobilisation within the past 3 months	3 (0·3%)	6 (0·4%)	8 (1·3%)
Surgery within the past 3 months	4 (0·3%)	7 (0·5%)	2 (0·3%)
Chronic cardiac failure	0 (0·0%)	2 (0·1%)	2 (0·3%)
Rheumatoid arthritis	4 (0·3%)	10 (0·7%)	4 (0·7%)
Chronic renal failure	2 (0·2%)	2 (0·1%)	0 (0·0%)
Chronic obstructive pulmonary disease	2 (0·2%)	7 (0·5%)	4 (0·7%)
Inflammatory bowel disease	5 (0·4%)	5 (0·3%)	1 (0·2%)
Chronic venous insufficiency	29 (2·5%)	88 (5·8%)	38 (6·3%)
Diabetes	16 (1·4%)	35 (2·3%)	17 (2·8%)
Type of trauma			
Fibula or tibia shaft fracture (or both)	19 (1·6%)	75 (5·0%)	34 (5·6%)
Tibial plateau fracture	2 (0·2%)	12 (0·8%)	3 (0·5%)
Achilles tendon rupture	13 (1·1%)	38 (2·5%)	10 (1·7%)
Bimalleolar or trimalleolar ankle fracture	6 (0·5%)	13 (0·9%)	4 (0·7%)
Single malleolar ankle fracture	83 (7·2%)	127 (8·4%)	32 (5·3%)
Patellar fracture	10 (0·9%)	14 (0·9%)	10 (1·7%)
Ankle dislocation, Lisfranc injury	59 (5·1%)	82 (5·4%)	18 (3·0%)
Severe knee sprain (with oedema or haemarthrosis)	13 (1·1%)	16 (1·1%)	22 (3·6%)
Non-severe knee sprain	80 (6·9%)	87 (5·8%)	37 (6·1%)
Severe ankle sprain	196 (16·9%)	288 (19·1%)	84 (13·9%)
Non-severe ankle sprain	424 (36·6%)	444 (29·5%)	224 (37·1%)
Patellar dislocation	7 (0·6%)	8 (0·5%)	4 (0·7%)
Tarsal or metatarsal bones or forefoot fracture	206 (17·8%)	254 (16·9%)	106 (17·6%)
Significant muscle injury	5 (0·4%)	6 (0·4%)	2 (0·3%)
Other	36 (3·1%)	41 (2·7%)	13 (2·2%)

(Table 1 continues on next page)

patients, the 3-month rate of symptomatic venous thromboembolism was 0·7% (95% CI 0·3–1·4; n=8/1159; table 2), which is lower than the prespecified cutoffs of 1% for the absolute rate and 2% for the upper 95% CI. Venous thromboembolism events are detailed in the appendix (p 4). In the per-protocol population, 123 patients were excluded during the interventional phase: 36 patients with a TRiP(cast) score less than 7 who received anticoagulant treatment, 12 patients with a TRiP(cast) score of 7 or more who did not receive an anticoagulant, and 75 who received an anticoagulant for a reason other than venous thromboembolism (appendix p 12). 1048 patients with a TRiP(cast) score less than 7 were included in the per-protocol population, in which the rate of symptomatic venous thromboembolism was 0·8% (95% CI 0·3–1·5; n=8/1048), which is lower than the prespecified cutoffs of 1% for the absolute rate and 2% for the upper limit of the 95% CI (appendix p 9).

In patients included in the intervention phase and having a TRiP(cast) score of 7 or more (n=346), the 3-month rate of symptomatic venous thromboembolism was 2·6% (95% CI 1·2 to 4·9, n=9/346). In the per-protocol population of high-venous thromboembolism risk patients, the venous thromboembolism rate was 2·7% (95% CI 1·2 to 5·0, n=9/334), despite anticoagulant treatment.

In the control phase, 304 (50·4%) of 603 patients received anticoagulation. In the intervention phase, 368 (24·5%) of 1505 patients were prescribed anticoagulants. The absolute difference between phases was –26·0 percentage points (95% CI –30·2 to –21·7; odds ratio 3·3 [95% CI 2·7 to 4·1]; p<0·0001; table 2). The median duration of anticoagulation treatment (left to the discretion of the physician) was 28 (IQR 17–32) days. Rates of anticoagulation according to centre and TRiP(cast) score are presented in the appendix (pp 6, 7). During the control phase, 184 (40·0%) of 460 patients with a TRiP(cast) score less than 7 received an anticoagulant, whereas 23 (16·1%) of 143 patients with a TRiP(cast) score of 7 or more did not receive prophylactic anticoagulant therapy. During the interventional phase, the rate of adherence to the TRiP(cast) score was 96·8% (95% CI 95·8 to 97·6; 1457/1505), with 36 (3·1%) of 1159 patients at low risk (TRiP(cast) score <7) treated and 12 (3·5%) of 346 patients at high risk (TRiP(cast) score ≥7) untreated. The intracluster correlation coefficient for this outcome was calculated as 0·1.

The cumulative rate of symptomatic venous thromboembolism was 1·0% (n=6/603) in the control phase and 1·1% (n=17/1505) in the intervention phase. The absolute difference between phases was 0·1 percentage points (95% CI –0·8 to 1·1; appendix pp 131–34).

No bleeding occurred during the control phase. One major bleed (spontaneous intracranial bleeding) and one clinically relevant non-major bleed (postoperative gastrocnemius muscle haematoma) occurred during the intervention phase. Neither of the patients involved were receiving anticoagulation as they were in the low-risk

group. The bleeding rate was 0·1% (n=2/1505; table 2). No incidence of heparin-induced thrombocytopenia was reported in this study.

The area under the receiver operating characteristic curve of the TRiP(cast) score was 0·78 (95% CI 0·71–0·85) with a Brier score of 0·01 (0·01–0·02; appendix pp 8, 9, 15). With a TRiP(cast) score threshold at 7, the sensitivity was 0·57 (0·34–0·77), the specificity was 0·77 (0·75–0·79), and the negative predictive value was 0·99 (0·99–1·00; appendix p 8). Similar results were obtained when anticoagulation was added as a variable in the model (appendix p 9).

Most physicians (n=1403/1462; 96·0%) were moderately or highly satisfied with the application used as a case report form and calculator of the TRiP(cast) score (rating ≥3 on a 5-level Likert scale; data were missing for 43 physicians).

Discussion

In this stepped-wedge, cluster-randomised trial of 2108 patients with lower limb trauma requiring immobilisation, a TRiP(cast) score of less than 7 identified a large subgroup of patients with a 3-month risk of venous thromboembolism below 1% when discharged home without prophylactic anticoagulation. This targeted anticoagulation strategy was associated with an absolute decrease of 26 percentage points in the rate of anticoagulant prescription as compared with current practice.

Previous trials assessing the benefit of anticoagulation reported disparate results.[4,21–24] Heterogeneity of these trials' inclusion criteria and endpoints could explain this discrepancy,[2,3,25] as well as the absence of consensus between international guidelines.[8,26] The last Cochrane meta-analysis concluded, with a moderate level of evidence, the efficacy of LMWH in preventing symptomatic venous thromboembolism in patients with lower limb immobilisation.[7] However, the authors recommended further research to personalise the decision for or against anticoagulation according to the type of trauma, immobilisation characteristics, and the risk factors of each patient.[2]

Several risk assessment models have been developed for this purpose.[9,10,27–29] Most of these models were based on expert consensus or were not prospectively validated in an implementation trial. The TRiP(cast) score is derived from the combination of the Leiden TRiP(cast) score, based on data of a case-control study, and the Trauma, Immobilisation and Patient Characteristics (TIP) score, developed by expert consensus.[10,27,29,30] Assessed retrospectively, the TRiP(cast) score performed better than the other models (ie, the Plymouth rule, the GEMNet guidelines, and the Aberdeen venous thromboembolism risk tool), but it required prospective validation in an implementation trial.[31]

In the present trial, the 3-month rate of symptomatic venous thromboembolism in patients at low risk according to the TRiP(cast) score was 0·7% with a 95% CI upper value of 1·4%, far below the cutoff of a 1% incidence rate with an upper 95% CI of less than 2%.[4] This rate of venous thromboembolism was lower than

	Primary analysis: intervention phase—patients with TRiP(cast) score <7 (n=1159)	Secondary analyses: intervention phase—intention-to-treat patients (n=1505)	Secondary analyses: control phase—intention-to-treat patients (n=603)
(Continued from previous page)			
Type of immobilisation			
Upper leg cast	7 (0·6%)	33 (2·2%)	8 (1·3%)
Lower leg cast	449 (38·7%)	704 (46·8%)	246 (40·8%)
Foot cast (ankle free) or any semi-rigid cast without plantar support	88 (7·6%)	110 (7·3%)	36 (6·0%)
Semi-rigid cast with plantar support	615 (53·1%)	658 (43·7%)	313 (51·9%)
Duration of casting (days)*	20 (10–28)	21 (10–28)	21 (10–32)
Anticoagulation			
No treatment	1123 (96·9%)	1135 (75·4%)	301 (49·9%)
Fondaparinux	4 (0·3%)	108 (7·2%)	122 (20·2%)
Low-molecular-weight heparin	32 (2·8%)	262 (17·4%)	178 (29·5%)
Direct oral anticoagulant	0 (0·0%)	0 (0·0%)	2 (0·3%)
Duration of anticoagulation (days)*	28 (17–32)	27 (10–42)	28 (14–42)
Surgery decided after discharge from emergency department	7 (0·6%)	10 (0·7%)	4 (0·7%)

Data are n (%) unless otherwise specified.*Data are median (IQR). †BMI values were missing for three patients. ‡The postpartum period was defined as the 6 weeks after birth.

Table 1: **Baseline characteristics**

	Intervention phase (N=1505)	Control phase (N=603)	Difference (95% CI)
Primary outcome			
Symptomatic venous thromboembolism in low-risk* patients	8/1159 (0·7%)	..	..
Secondary outcomes			
Anticoagulant prescription rate	368 (24·5%)	304 (50·4%)	–26·0 (–30·2 to –21·7)
Venous thromboembolism rate at 3 months	17 (1·1%)†	6 (1·0%)	0·1 (–0·8 to 1·1)
Venous thromboembolism rate at 3 months in low-risk patients	8/1159 (0·7%)	2/460 (0·4%)	0·3 (–0·2 to 0·5)
Venous thromboembolism rate at 3 months in high-risk patients	9/346 (2·6%)	4/143 (2·8%)	–0·02 (–0·3 to 0·3)
Fatal pulmonary embolism	0	0	..
Unexplained sudden death	0	1 (0·2%)	..
Symptomatic pulmonary embolism	2 (0·1%)	0	..
Symptomatic proximal deep vein thrombosis	2 (0·1%)	1 (0·2%)	..
Symptomatic distal deep vein thrombosis	11 (0·7%)	4 (0·7%)	..
Major bleeding	1 (0·1%)	0	..
Clinically relevant non-major bleeding	1 (0·1%)	0	..

Data are n (%) or percentage points change (95% CI). Analysis was in the intention-to-treat population. *Patients at low risk of thromboembolism were identified by a TRiP(cast) score under 7; patients at high risk were identified by a score of 7 or more. †Little information on symptomatic deep vein thrombosis, as defined by the adjudication committee, was available for two patients (no ultrasound results).

Table 2: **Primary and secondary outcomes**

those observed in both groups of the randomised controlled POT-CAST trial, comparing LMWH versus no anticoagulant in patients with lower limb trauma and a plaster cast—namely, 1·4% (95% CI 0·7–2·5) in treated patients and 1·8% (1·0–3·1) in those not receiving LMWH.[4] In our trial, targeting prophylactic anticoagulant based on the TRiP(cast) score, although decreasing the rate of anticoagulant use by half, did not significantly increase the overall incidence of symptomatic venous thromboembolism. This strategy appears doubly beneficial by avoiding prophylactic anticoagulation in patients at low risk of venous thromboembolism and by reserving this treatment for patients at high risk.

Current practices vary widely between centres and probably between practitioners, at least in France and Belgium. This variance led to 16% of patients at high risk of venous thromboembolism according to their TRiP(cast) score not receiving prophylactic anticoagulation and, conversely, 40% of patients at low risk receiving an anticoagulant in current practice.

Notably, the thromboembolic event rate remained high (2·7%) in patients with a TRiP(cast) score of 7 or more despite prophylactic anticoagulation. This result substantiates that a small subgroup of patients with lower limb trauma and immobilisation is at high risk of venous thromboembolism, necessitating thromboprophylaxis, and suggests that current prophylactic anticoagulation with LMWH or fondaparinux might not be sufficient in these patients. Direct oral anticoagulants could be a more effective option. In a network meta-analysis, rivaroxaban was ranked first in terms of effectiveness as compared with LMWH, aspirin, and fondaparinux, without causing a substantial increase in the risk of bleeding.[3] In our study, the rate of bleeding was very low, reinforcing the potential net clinical benefit of direct oral anticoagulants in patients with lower limb trauma at high risk of venous thromboembolism.

This study provides a high level of evidence for future recommendations and changes in practice. Use of the TRiP(cast) score model to individualise anticoagulant treatment rather than an overall population-based approach has several major effects. In countries such as France and Belgium, where thromboprophylaxis is widely used, this strategy avoids unnecessary anticoagulation treatment and subsequent bleeding risk, as well as the negative effect of daily subcutaneous injections on quality of life. Considering the frequency of lower limb traumas (~6000 ankle sprains per day and 85 000 lower limb fractures per year in France) and the large proportion of patients at low risk of thromboembolism who can be identified with a simple clinical tool, implementation of the TRiP(cast) score should lead to a substantial decrease in the cost of care.[32,33] Conversely, in countries where prophylactic anticoagulation of patients with lower limb trauma and immobilisation is not current practice, targeted treatment according to the TRiP(cast) score could be a cost-effective way to reduce the burden of venous thromboembolism.

The CASTING study has several limitations. The first limitation relates to the design of this study. The study was not fully blinded. In the intervention phase, both the physician and the patient knew that the TRiP(cast) score was being applied to target anticoagulation. However, the primary outcome was assessed by an independent adjudication committee that was blinded to the study phase. Second, the primary outcome was assessed in part of the included population and the primary analysis was uncontrolled, the upper limit of the 95% CI of the venous thromboembolism rate being compared with a prespecified cutoff point. The endpoint comparing the overall rates of venous thromboembolism was a key secondary outcome and showed no difference. Third, despite a high telephone follow-up rate of 93·2%, some patients could only be followed up through consultation of their electronic records and registrations of death. The characteristics of patients without telephone follow-up were similar to those of patients analysed as a whole. The fourth limitation is the stepped-wedge process, which did not allow a uniform recruitment between phases and centre. This design led to inclusion of an insufficient number of patients in some cluster phases, which led to the grouping of two centres. Consequently, we could not account for the phase random effect in addition to the cluster random effect in the statistical analysis.[34] Fifth, the rate of patients receiving prophylactic anticoagulation according to current practice, and consequently the benefit of TRiP(cast) score implementation in terms of overall anticoagulation rate, might differ according to country and centre. Sixth, demographic data on race or ethnicity were not collected. Finally, the satisfaction with the application assessment was more related to the study data collection form than to the TRiP(cast) score.

These findings suggest that, in emergency department patients with a lower limb trauma requiring immobilisation, prophylactic anticoagulation can be safely withheld in patients with a TRiP(cast) score less than 7, with a very low risk of venous thromboembolism at 3 months. Compared with current practices in France and Belgium, implementation of the score to target anticoagulation towards patients at high risk of thromboembolism was associated with a substantial reduction in the rate of anticoagulant prescriptions without significant increase in the overall rate of venous thromboembolism.

Contributors

DD, AP, DV, J-JB, JR, TM, DS, and P-MR conceived and designed the study. All authors were responsible for the acquisition, analysis, or interpretation of data. DD, AP, JR, and P-MR drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. JR and DD did the statistical analysis. DD, AP, JR, and P-MR obtained funding. DD, DV, J-JB, AA, MH, EM, FB, CB, SL, TD, PV, LS, NM, and P-MR provided administrative, technical, or material support. DD, AP, DV, DS, TM, and P-MR supervised the study.

Declaration of interests
AP reports receiving personal fees from Daiichi, Bayer, Bristol Myers Squibb, Pfizer, Stago, Alnylam, Sanofi, Viatris, Boehringer, and Leo Pharma. SL reports receiving personal fees from Brahms. TD reports receiving personal fees from Sanofi Aventis. TM reports receiving personal fees from Bristol Myers Squibb. P-MR reports receiving personal fees from Aspen, Bayer, Boehringer Ingelheim, Sanofi Aventis, Pfizer, Bristol Myers Squibb, and Viatis. All other authors declare no competing interests.

Data sharing
Qualified investigators can request access to the patient-level study data that underlie the results presented in this publication. Other study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and dataset specifications can also be made available. Patient data will be anonymised and study documents will be redacted to protect the privacy of study participants. All applications must be submitted to the corresponding author for assessment by an independent scientific review committee. Once the sharing agreements have been signed, a secure link will be set up for a short period.

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