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

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Individualized thromboprophylaxis in patients with lower-leg cast immobilization - a validation and subgroup analysis in the POT-CAST trial

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ABSTRACT

Background A small subgroup of patients treated with lower-leg cast immobilization develops Venous Thromboembolism (VTE).

Objectives 1. Identify risk factors for VTE in patients with cast immobilization, 2. Assess the effectiveness of thromboprophylaxis in low- and high-risk groups, 3. Validate the performance of the L-TRiP(cast) score.

Methods Data from the POT-CAST trial were used. 1519 patients with lower-leg cast immobilization were randomized to a prophylactic dose of low-molecular-weight-heparin or no treatment. Primary outcome: symptomatic VTE within 3-months. Absolute risks (AR) were determined for low- and high-risk subgroups. For several risk factors, relative risks (RR) for VTE were estimated with corresponding 95%CIs. For validating the L-TRiP(cast) score, a discrimination and calibration analysis were performed.

Results Patients with a body mass index >30kg/m2 and those with a VTE in their family history had an increased VTE risk, RR 3.8, (95%CI 1.5 - 9.4) and RR 2.4 (95%CI 1.0 - 5.6), respectively. Concerning injury-specific risk factors, patients with an Achilles tendon rupture or those who were surgically treated had the highest risk of VTE, AR at 8.5% (95%CI 3.7 – 16.1) and AR 3.5% (95%CI 1.3 – 7.5), respectively. There were no subgroups in which thromboprophylaxis was effective for prevention of symptomatic VTE. The AUC for the L-TRiP(cast) score was 0.69 (95%CI 0.58 – 0.80).

Conclusions Thromboprophylaxis was not effective for VTE prevention following lower-leg cast immobilization in any risk category. Low- and high-risk individuals could be identified using the L-TRiP(cast) score. The best treatment strategy for these patients is yet to be determined.

INTRODUCTION

Patients treated with lower-leg cast immobilization still develop Venous Thromboembolism (VTE) (consisting of deep vein thrombosis [DVT] or pulmonary embolism [PE]) despite the administration of thromboprophylaxis.[1] Each year, approximately 3.5 million patients are treated with a lower-leg cast worldwide, therefore the burden of VTE is considerable with an estimated number of 56 000 VTEs due to this situation.[1]

In the POT-CAST trial (Prevention Of Thrombosis following lower-leg CAST immobilization), the overall risk of symptomatic VTE was 1.6% (n=1435) within 3-months following lower-leg cast immobilization. A prophylactic dose of low-molecular-weight-heparin (LMWH) (2850 IU once daily for patients <100kg, double dose >100kg, for the total duration of cast immobilization) was not effective for VTE prevention (absolute risk reduction -0.4%, 95% Confidence Interval (CI) -1.8 to 1.0).[2] Hence, new treatment strategies should be established in order to reduce the number of VTEs and to prevent chronic complications such as a post-thrombotic syndrome. A fairly simple approach would be to increase the duration or dose of thromboprophylaxis. However, if we would treat all patients, this may introduce an excess of bleeding events outweighing the number of prevented VTEs. Concomitantly, daily LMWH injections are unpleasant and associated with higher costs compared with no treatment. Therefore, individualized therapy might be a better strategy, in which thromboprophylaxis could be withheld in low-risk individuals whereas a higher dose could be administered in high-risk individuals.

To classify patients as high-risk individuals, some risk factors have been identified in previous studies. Besides classical risk factors like older age[3] and the use of oral contraceptives[4], cast-specific risk factors such as a non-weight bearing cast[5-7] or rigid immobilization[7,8] have been shown to be associated with increased VTE risk. In addition, injury-specific factors such as fracture[9,10] (versus soft tissue injury), severe injury[7] or traumatic injury increase thrombosis risk.[4] In addition to identification of risk factors in individuals, high-risk patients can be identified by use of a prognostic model for VTE risk, in which all such factors are combined. Previously, we developed and validated the L-TRiP(cast) score (Leiden-Thrombosis Risk Prediction) and showed that VTE risk prediction in lower-leg cast patients is feasible and leads to good discrimination. However due to the case-control setting, absolute risks could not be determined.[11] No other prediction models for VTE risk following lower-leg cast immobilization have been validated in this setting.

To explore whether individualized therapy is an option to improve prevention of VTE, we aimed to 1. Identify risk factors for VTE within the POT-CAST trial, 2. Assess the effectiveness of thromboprophylaxis within low- and high-risk groups and 3. Validate the performance of the L-TRiP(cast) score.

METHODS

Study Design

For this study we used data of the POT-CAST trial of which details have been published previously.[2] In short, the POT-CAST study is a pragmatic multicentre, randomized, controlled, open-label trial with blinded outcome evaluation designed to study the effectiveness of LMWH for the prevention of VTE following lower-leg (below the knee) cast immobilization. Patients with a traumatic injury of the leg or foot who were treated with a lower-leg cast for at least 1 week were eligible for inclusion. Those with a personal history of VTE or women who were pregnant were not allowed to participate. 1519 patients were randomized (1:1) to either a prophylactic dose of LMWH (2850IU administered subcutaneously, treatment group) or to no treatment (control group). The primary outcome was the occurrence of a symptomatic VTE within 3 months after inclusion and the primary safety outcome was the occurrence of major bleeding (according to the ISTH criteria[12]) within the same time frame. Patients were not screened for the occurrence of asymptomatic VTE.

Data Collection and Laboratory Analysis

Injury-specific data were collected upon inclusion and derived from an individuals' electronic patient record. In addition, patients were asked to complete a questionnaire (digital [online] or postal) on thrombotic risk factors (such as age, sex, use of oral contraceptives, cancer) shortly after inclusion in the trial. Furthermore, we collected data on the study outcomes, cast application (duration, complications) and treatment adherence using two additional questionnaires, and one final telephone interview, throughout follow-up.

Blood was drawn in vacuum tubes containing 0.105M sodium citrate in all patients upon presentation at the emergency department (before any administration of thromboprophylaxis). All blood samples were centrifuged at 2500g for 10 minutes at 18°C, thereafter, following aliquoting, the samples were stored at −80°C within 4 hours of venepuncture. We measured coagulant factor VIII, factor XI and Von Willebrand factor levels using the TOP analyser (Werfen Instrumentation Laboratory, Barcelona, Spain). DNA analysis for the FV Leiden mutation (rs6025) and the prothrombin G20210A mutation (rs1799963) was performed using a combined polymerase chain reaction method with the TaqMan assay. Blood group polymorphisms were determined by a 5' nuclease assay (Taqman; Applied Biosystems, Foster City, CA, USA) using a PCR reaction mix (Taqman Genotyping Master Mix, Applied Biosystems) and an allele-specific fluorescent probe equipped with a minor groove binding moiety (Applied Biosystems).

Statistical Analysis

After exclusion of patients who had not met the inclusion criteria (or had exclusion criteria), patients who were lost to follow-up or those who withdrew consent, 1435 patients were included in the intention-to-treat population and considered for the current analyses. We calculated absolute risks (AR) for several low- and high-risk subgroups by estimating the cumulative incidence for VTE within 3-months with corresponding 95%CI. In an intention-to-treat analysis, the effectiveness of LMWH for VTE prevention within subgroups was determined by comparing cumulative incidences between the treatment and control group which yielded absolute risk differences (RD) and relative risks (RR) with 95%CIs. For risk factor identification, a similar analysis was performed comparing the cumulative incidences between risk groups. All subgroup analyses were post-hoc analyses and not stated in the original study protocol. However, since the POT-CAST trial showed no effectiveness on a population level, targeting low- and high risk groups seems prompted.

For validation of the L-TRiP(cast) model we assessed discrimination and calibration. Discrimination is a statistic to assess how well a model can distinguish a case from a control (given a pair that consists of a case and control) whereas calibration shows the concordance between the observed risks and the risks as predicted by the model. For a small number of participants (12%), risk factor data were missing. Since only 23/1435 patients developed a VTE, we performed a multiple imputation technique to maintain power for the validation analysis (10 imputations, results were pooled according to Rubins' rules).[13] Following imputation, in a discrimination analysis, we calculated the L-TRiP(cast) score per individual, after which the absolute risk was estimated with corresponding 95%CI (per two points to account for the small event number). For each cut-off we calculated the sensitivity and specificity of the L-TRiP(cast) score and subsequently the Area Under the Curve (AUC) by modelling a Receiver Operating Characteristic (ROC) curve. Second, we fitted the L-TRiP(cast) score in a logistic regression model to obtain a new constant (baseline risk) as this lacked in the development of the L-TRiP(cast) score (because this model was developed using case-control data). Thereafter, we estimated the predicted risk for VTE per individual using the L-TRiP(cast) score which was compared with the observed risk and plotted in a calibration plot.[14]

Finally, we compared the performance of the L-TRiP(score) with two other models designed to predict VTE risk following cast-immobilization, i.e., the full and restricted model (all shown in *Supplement Table 1*). The full and restricted model were developed in addition to the L-TRiP(cast) score) to assess whether the inclusion of biomarkers improved predictive performance.[11] The full model consist of 32 predictors including 3 genetic and 6 biomarker predictors, whereas the restricted model consists of 11 predictors with 2 genetic and 1 biomarker predictors. While in the derivation data, the full and restricted model performed best, the L-TRiP(cast) score was developed to use in clinical practice (no need for blood sampling). For the full model, monocyte percentage, total cysteine and red cell distribution width were not available, but all other biomarkers/genetics (FVIII activity, FXI activity, vWF antigen level, prothrombin mutation, factor V Leiden mutation and ABO blood type) were measured. We compared AUC values and sensitivity and specificity statistics. As the full and restricted model included tertiles of coagulation factors levels (VWf, factor VIII and factor XI) that were based on population data, we checked whether updating the cut-offs of these tertiles to levels of the POT-CAST population improved performance. We expected coagulation factor levels to be increased after trauma, and anticipated on improved performance.

All analyses were performed with the use of IBM SPSS Statistics software for Windows, version 23 (SPSS), and Stata software, version 14 (StataCorp).

RESULTS

Study population and POT-CAST main result

Table 1 shows baseline characteristics of the POT-CAST trial. 1435 were included in the analyses, mean (SD) duration of cast immobilization was 4.9 (2.5) weeks. LMWH prophylaxis was not effective to prevent VTE within 3-months following lower-leg cast immobilization, either in the intention-to-treat or the per-protocol analysis. In the treatment group (LMWH prophylaxis) 10/719 patients developed VTE versus 13/716 patients in the control group (risk difference (RD) -0.4% (95%CI -1.8 to 1.0). No major bleeding occurred in either group.

Table 1: Characteristics of study population.

Patient characteristics §	**Treatment group*** **(n=719)**	**Control group** **(n=716)**
Male sex, no./total no. (%)	347/719 (48.3)	369/716 (51.5)
Mean age, years	46.5±16.5	45.6±16.4
Mean BMI, kg/m^2 †	26.0±4.4	25.7±4.4
Smoking, no./total no. (%)		
Current	173/663 (26.1)	178/665 (26.8)
Ever	188/663 (28.4)	178/665 (24.9)
Oral contraceptives use, no./total no. (% of women)	64/348 (18.4)	41/326 (12.6)
Paid employment (%)	442/664 (66.6)	469/469 (65.5)
Cancer		
Within last year	8/674 (1.2)	9/674 (1.3)
More than 1 year ago	26/674 (3.9)	20/674 (3.0)
Family history of venous thromboembolism, no./total no. (%) ‡	67/638 (10.6)	56/635 (9.4)

* Low Molecular Weight Heparin, either Nadroparin or Dalteparin.
§ Percentages of complete data, BMI data were missing for 112 patients
† BMI: body mass index in kilogram divided by the square of the height in meters.
‡ First degree relatives

Low- and high-risk groups

Table 2a shows absolute risks within all low- and high-risk groups. Men had a similar risk compared with (all) women (AR 1.9% [95%CI 1.1 – 3.3] versus 1.3% [95%CI 0.6 – 2.4]), for an RR of 1.6 (95%CI 0.7 - 3.7). Women using oral contraceptives had an exact similar risk as men (AR 1.9% [95%CI 0.2 – 6.7]). Patients with classical VTE risk factors such as a body mass index above 30 kg/m^2 or a positive family history of VTE had an increased risk of VTE, i.e., RR 3.8 (95%CI 1.5 - 9.4) and RR 2.4 (95%CI 1.0 - 5.6), respectively. Patients with cast immobilization for an Achilles tendon rupture developed VTE in 8.5% (95%CI 3.7-16.1), 4/21 (19.0%) patients who underwent surgery for Achilles tendon repair developed symptomatic VTE compared with 4/73 (5.5%) who were conservatively treated). Immobilization for fractures was associated with a lower risk than Achilles tendon ruptures (1.1% for metatarsal fractures and 1.2% for ankle fractures). Surgically treated injuries led to a higher VTE risk than conservatively treated injuries, AR 3.5% (95%CI 1.3 – 7.5) and 1.3% (95%CI 0.8 – 2.1), respectively (OR 2.7 [95%CI 1.0 - 6.9]). Patients with cast immobilization ≥ 6 weeks had a VTE risk of 1.5% (95%CI 0.7 – 2.7).

The effectiveness of LMWH in all subgroups is shown in *Table 2b*. There were no risk groups in which thromboprophylaxis significantly reduced symptomatic VTE. RRs between the treatment and control group ranged from 0.3 (95%CI 0.1 – 1.3) in women to 2.3 (95%CI 0.6 to 8.9) in patients with an Achilles tendon rupture. Overall, similar RDs were found (though with wide confidence intervals) as compared with the main RD in the entire trial population: RD -0.4 (95%CI -1.8 to 1.0).

Validation of the L-TRiP(cast) score

The L-TRiP(cast) model (score shown in *Table 3*) performed well with an AUC of 0.69 (95%CI 0.58 to 0.80) (*Table 4*). The Full model and Restricted model performed better with an AUC of 0.76 and 0.75 respectively. Updated coagulation factor tertiles (based on the tertile distribution in POT-CAST data) led to a further improvement of discriminative performance. *Table 5* shows sensitivity, specificity and absolute risk data for a range of L-TRiP(cast) scores. The absolute VTE risk increased with higher L-TRiP(cast) score. For example, patients with a risk score of 8-9 had a 1.6% risk while those with a score of 10 to 11 had a 2.8% risk for VTE. Using a cut-off score of at least 8, the sensitivity was 75% with a specificity of 46%. In the calibration plot (*Figure 1*), a good concordance between the observed and predicted probability for VTE is shown.

Table 2a Absolute VTE risk in subgroups of the POT-CAST trial.

	no. of patients*	no. of VTEs	Absolute VTE Risk % (95%CI)	Relative Risk (95%CI)†
Main outcomes				
Primary outcome: venous thromboembolism	1435	23	1.6 (1.0 - 2.4)	na
Primary safety outcome: major bleeding	1435	0	0 (0 - 0.3)	na
VTE risk factors				
Women	719/1435	9	1.3 (0.6 - 2.4)	ref
Men	717/1435	14	1.9 (1.1 - 3.3)	1.6 (0.7 - 3.7)
<55 years	697/1435	12	1.7 (0.8 - 3.0)	ref
≥55 years	461/1435	11	2.4 (1.2 - 4.2)	2.1 (0.9 - 4.9)
≥75 years	52/1435	0	0.0 (0.0 - 6.8)	na
Body Mass Index <30 kg/m²	1131/1335	12	1.1 (5.5 - 1.8)	ref
Body Mass Index ≥30 kg/m²	204/1335	8	3.9 (1.7 - 7.6)	3.8 (1.5 - 9.4)
No VTE in family history	1149/1273	15	1.3 (0.7 - 2.1)	ref
VTE in family history	123/1273	4	3.2 (0.9 - 8.1)	2.4 (1.0 - 5.6)
Use of oral contraceptives	105/1390	2	1.9 (0.2 - 6.7)	1.2 (0.2 - 5.3)
Injury specific factors ‡				
Metatarsal fractures	532/1435	6	1.1 (0.4 - 2.4)	ref
Ankle fractures	497/1435	6	1.2 (0.4 - 2.6)	1.0 (0.3 - 3.3)
Achilles tendon ruptures	94/1435	8	8.5 (3.7 - 16.1)	8.2 (2.8 - 24.1)
≥6 weeks cast immobilization	672/1435	10	1.5 (0.7 - 2.7)	0.9 (0.4 - 2.0)
Conservatively treated	1265/1435	17	1.3 (0.8 - 2.1)	ref
Surgically treated	170/1435	6	3.5 (1.3 - 7.5)	2.7 (1.0 - 6.9)

na denotes not applicable, ref denotes reference.
*Denominator indicates the number of patients in which subgroup data were available.
† Relative Risks for VTE for each risk factor.
‡ Relative Risk for ankle fractures or Achilles tendon ruptures versus metatarsal fractures.
≥6 weeks immobilization versus <6 weeks.

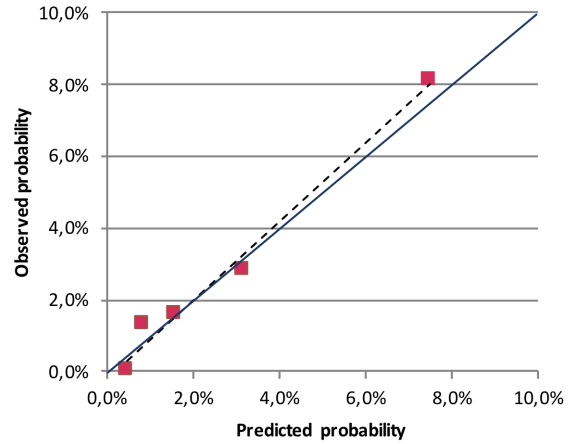

Figure 1: Calibration plot for the L-TRiP(cast) score.
Depicting the predicted versus the observed probability for venous thromboembolism (VTE) risk following cast immobilization. Dots represent risks for L-TRiP(cast) score categories 4–5, 6–7, 8–9, 10–11, and 12–17. Dashed line represents calibration line with slope 1.09.

Table 2b Efficacy of LMWH in subgroups of the POT-CAST trial.

	Treatment Group (n=719)			Control Group (n=716)			Efficacy	Efficacy
	no. of patients*	**no. of VTEs**	**Absolute Risk % (95%CI)**	**no. of patients***	**no. of VTEs**	**Absolute Risk % (95%CI)**	**Relative Risk (95%CI)**	**Absolute Risk Difference % (95%CI)**
Main outcomes								
Primary outcome: venous thromboembolism	719	13	1.4 (0.7 - 2.5)	716	10	1.8 (1.0 - 3.1)	0.8 (0.3 - 1.7)	-0.4 (-1.8 - 1.0)
Primary safety outcome: major bleeding	719	0	0 (0 - 0.8)	716	0	0 (0 - 0.5)	Not estimable	0 (-0.5 - 0.5)
VTE risk factors								
Women	372/719	2	0.5 (0.1 - 1.9)	347/716	7	2.0 (0.8 - 4.1)	0.3 (0.1 - 1.3)	-1.5 (-3.1 - 0.2)
Men	348/719	8	2.3 (1.0 - 4.5)	369/716	6	1.6 (0.6 - 3.5)	1.4 (0.5 - 4.0)	0.7 (-1.4 - 2.7)
<55 years	482/719	6	1.2 (0.5 - 2.7)	485/719	6	1.2 (0.5 - 2.7)	1.0 (0.3 - 3.1)	0.0 (-0.1 - 0.1)
≥55 years	237/719	4	1.7 (0.5 - 4.3)	224/716	7	3.1 (1.3 - 6.3)	0.5 (0.2 - 1.8)	-1.4 (-4.2 - 1.4)
≥75 years	28/719	0	0.0 (0.0 - 12.3)	24/716	0	0.0 (0.0 - 14.2)	Not estimable	Not estimable
Body Mass Index >30 kg/m^2	113/665	4	3.5 (1.0 - 8.8)	91/670	4	4.4 (1.2 - 10.9)	0.8 (0.2 - 3.1)	-0.9 (-6.3 - 4.6)
VTE in family history	67/638	2	3.0 (0.4 - 10.4)	56/635	2	3.6 (0.4 - 12.3)	0.8 (0.1 - 5.7)	-0.6 (-6.9 - 5.8)
Use of oral contraceptives	64/695	1	1.6 (0.0 - 8.4)	41/695	1	2.4 (0.1 - 12.9)	0.6 (0.0 - 10.0)	-0.9 (-6.5 - 4.7)
Injury specific factors								
Metatarsal fractures	277/719	2	0.7 (0.1 - 2.6)	255/716	4	1.6 (0.4 - 4.0)	0.5 (0.1 - 2.5)	-0.8 (-2.7 - 1.0)
Ankle fractures	255/719	3	1.2 (0.2 - 3.4)	242/716	3	1.2 (0.3 - 3.6)	0.9 (0.2 - 4.7)	-0.1 (-2.0 - 1.9)
Achilles tendon ruptures	40/719	5	12.5 (4.2 - 26.8)	54/716	3	5.6 (1.2 - 15.4)	2.3 (0.6 - 8.9)	6.9 (-5.0 - 18.9)
≥6 weeks cast immobilization	336/719	3	0.9 (0.2 - 2.6)	336/716	7	2.1 (0.8 - 4.2)	0.4 (0.1 - 1.6)	-1.2 (-3.0 - 0.6)
Conservatively treated	628/719	6	1.0 (0.4 - 2.1)	637/719	11	1.7 (0.9 - 3.1)	0.6 (0.2 - 1.5)	-0.8 (-2.0 - 0.5)
Surgically treated	91/719	4	4.4 (1.2 - 10.9)	79/716	2	2.5 (0.3 - 8.8)	1.7 (0.3 - 9.2)	1.9 (-3.6 - 7.3)

*Denominator indicates the number of patients in which subgroup data were available

Table 3: L-TRiP(cast) score.

Predictor variable	Point value
Age ≥ 35 and < 55 years	2
Age ≥ 55 years	3
Male sex	1
Current use of oral contraceptives	4
Cancer within the past 5 years	3
Pregnancy or puerperium	3
BMI ≥ 25 and < 35 kg/m^2	1
BMI ≥ 35 kg/m^2	2
Pneumonia	3
Family history of VTE (first-degree relative)	2
Comorbidity (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	1
Hospital admission within the past 3 months	2
Bedridden within the past 3 months	2
Surgery within the past 3 months	2
Superficial vein thrombosis	3
Plaster cast: Complete leg	5
Plaster cast: Circular knee cast (ankle free)	2
Plaster cast: Foot	2
Plaster cast: Lower-leg	4

Table 4: Validation of the L-TRiP(cast) score in the POT-CAST study.

Model	AUC	95% CI	Intercept	Beta
Full model	0.76	0.68 - 0.84	-8,466	0,727
*Coagulation factors updated**	0.78	0.70 - 0.86	-7,540	0,552
Restricted model	0.75	0.68 - 0.83	-7,552	0,661
*FVIII updated**	0.77	0.70 - 0.84	-7,345	0,669
L-TRiP(cast) score	0.69	0.58 - 0.80	-7,089	0,352

*Updated models: using biomarker tertiles based on POT-CAST data

Table 5: L-TRiP(cast) performance in the POT-CAST study.

L-TRiP(cast) score cutoff ≥	Sensitivity	Specificity	L-TRiP(cast) score	No VTE*	VTE*	Absolute Risk
4	100%	0%	4-5	214,20	0,00	0,0%
5	100%	3%				
6	100%	15%	6-7	437,70	5,70	1,3%
7	91%	27%				
8	75%	46%	8-9	546,50	8,70	1,6%
9	59%	71%				
10	37%	85%	10-11	164,30	4,60	2,8%
11	22%	92%				
12	17%	97%	12-17	49,30	4,00	8,1%
13	13%	99%				
14	4%	99%				
15	4%	100%				
16	4%	100%				
17	4%	100%				

*Pooled result, therefore absolute numbers include decimals

DISCUSSION

In this study we assessed the risk for VTE following cast immobilization of the lower-leg in several subgroups within the POT-CAST trial. Overall, 1.6% developed a symptomatic VTE within 3-months following cast-application. Patients with a BMI ≥30 kg/m^2 and those with a family history of VTE showed to have an increased risk for VTE. Some injury-specific risk factors were identified such as having an Achilles tendon rupture or undergoing surgical treatment. LMWH was not effective for symptomatic VTE prevention in any subgroup. In addition, we validated the L-TRiP(cast) score which showed good discrimination and calibration. The VTE risk in the lowest risk category was 0.0% (4-5 points) and 8.1% in the highest risk category (12-17 points) indicating that high risk individuals can be identified using this score.

In the POT-CAST trial we demonstrated a lack of effectiveness of thromboprophylaxis for the prevention of symptomatic VTE following cast immobilization. In contrast, a recent Cochrane review on this topic showed effectiveness of LMWH for prevention of VTE following cast immobilization.[15] However, in this review, the conclusion was downgraded due to risk of bias and imprecision of results. The authors concluded that "future research might give more directives on specific thromboprophylaxis advice for different patients or patient groups, based on patient and trauma characteristics". A similar advice followed from another meta-analysis on this topic.[16] As VTE still occurs in about 1-2% of individuals, a new preventive strategy is necessary. Such a strategy could be to identify high-risk individuals based on the assessment of one or more risk factors. However, due to the relatively low incidence of VTE following cast immobilization, differences in study outcomes (asymptomatic versus symptomatic VTE) and restricted inclusion criteria (for example exclusion of surgically treated patients or tendon ruptures) there is much variation in the literature on risk factors in these patients.[17] In 2007, Riou and colleagues performed an observational cohort study in which 3 698 patients with nonsurgical isolated lower-limb injuries were screened for the occurrence of asymptomatic VTE upon cast removal (incidence 6.4%).[7] It was found that age>50 years old, rigid immobilization, non-weight bearing cast and severe injury (classified as any injury with fracture or dislocation or a complete tendon rupture) were all associated with asymptomatic VTE. However, having a family history of VTE or a BMI>30 kg/m^2 was not associated with higher VTE risk. Of note, thromboprophylaxis was often administrated in high-risk individuals, which may have affected the association with asymptomatic VTE. In contrast, in the POT-CAST trial these classical risk factors for VTE were found to be associated with a higher VTE risk.[2] A similar result was shown in 1993 in one of the first trials on thromboprophylaxis following lower-leg cast immobilization.[9] According to this trial, patients who did not develop thrombosis had on average 1.24 risk factors as compared

with 1.96 in those patients who did. Moreover, patients who developed a thrombosis under thromboprophylaxis had an average of 2.7 risk factors. A similar pattern was found in more recent data from a large population-based case-control study.[4] Patients with additional risk factors next to lower-leg cast immobilization such as the use of oral contraceptives, obesity, Factor V Leiden mutation, Non-O blood type or having a traumatic injury had an increased symptomatic VTE risk.

Interestingly, in the POT-CAST data, patients with Achilles tendon rupture (ATR) had a remarkably high risk of VTE (8.5%, 95%CI 3.7-16.1) while thromboprophylaxis was not effective. Varying sizes of risk have been described in earlier studies: a cohort study that collected data on all ATR during 12 consecutive years from one centre (n=945) showed an incidence of 1.4% within 4-5 months from start of treatmen7[18], while in another prospective cohort study in 291 patients with ATR (managed with full weight bearing in a walker boot) the incidence of VTE events was 4.8%.[19] In another small retrospective study, prompted by the authors' observations in clinical practice on this association, the incidence of VTE was 6.8% in 88 patients who were surgically treated for an ATR.[20] The underlying mechanism for this high risk remains to be elucidated. The long duration of immobilization could contribute, however, patients with >6 weeks of cast immobilization for other indications did not have a higher VTE risk in the POT-CAST trial. Another possibility might be that ATRs are initially treated with a non-weight bearing cast, perhaps leading to extra stasis in the veins. Unfortunately, in the POT-CAST trial, no information was present on the presence or absence of weight-bearing casts.

Identifying patients at high-risk based on one or more risk factors does not necessarily result in accurate risk prediction, this was recently shown by a large systematic review on this topic.[17] Due to the high frequency of many risk factors, the majority of patients will be classified as high-risk patients because they have one or more risk factors. A score that integrates information on all risk factors should be more useful. For this reason, in this study, the earlier developed L-TRiP(cast) score was validated which showed promising results. The Full and Restricted model, both including biomarkers such as factor V Leiden mutation and FVIII activity reached a higher AUC than the score, indicating better discrimination. By updating tertiles of all coagulation factors included in both models risk prediction further improved. This indicated that the level of biomarkers (such as FVIII activity) measured upon presentation at the emergency department greatly contributes to risk prediction following injury. However, determining biomarkers in patients with lower-leg cast immobilization upon presentation at the emergency department is not straightforward and in addition, costly. Since the L-TRiP(cast) score performed well, this might be used by clinicians to identify high-risk individuals. Yet, as thromboprophylaxis lacked effectiveness in any high-risk group, and the risk for major bleeding was negligible, there is a need for

future studies on a more stringent prevention strategy (for example a longer duration, higher dosage or stronger anticoagulant) in these groups. These studies may determine which patients can be withheld from treatment and for whom thromboprophylaxis needs to be intensified (i.e. define low- and high-risk categories).

The main strength of the POT-CAST trial is its size, as the largest randomized study into the effectiveness of LMWH for VTE prevention following cast immobilization of the lower-leg. By using these data, we were able to calculate absolute risks for different subgroups. Additionally, follow up was almost complete (98%) and few data on risk factors were missing. Furthermore, in POT-CAST only clinically relevant symptomatic VTEs were considered as an endpoint, making results of this study worthwhile for clinical practice. The current analysis also may have some limitations. First, none of the subgroup analyses were predefined as the trial was not powered to perform such analyses. Yet, as the main trial outcome showed no effectiveness for VTE prevention, the need for risk factor and individual risk assessment increased, allowing us to perform these analyses. Second, the low number of VTEs (n=23) limited precision of incidence estimations and validation statistics, however, by using a near complete dataset with complete follow-up and low number of missing risk factors the loss of precision was reduced to a minimum. Third, in general, patients who participate in clinical trials are somewhat younger and healthier as compared to the target population. For the POT-CAST trial this doesn't seem to be the case. Compared with a large cohort on the incidence of VTE following isolated lower-leg immobilization[7], patients in POT-CAST were older and had a higher BMI, indicating no selection of healthy patients. Finally, patients with a history of VTE were not included in the POT-CAST trial, for which reason the results are not applicable to these patients. However, as the absolute risk of VTE in this population is high[21], one may argue that these patients need prophylaxis in all circumstances.

Conclusion

VTE risk following cast application is 1.6% within 3-months. Patients with additional classical VTE risk factors such as high body mass index or having a family history of VTE have a higher risk to develop symptomatic VTE. Furthermore, patients with an Achilles tendon rupture, or patients who are surgically treated have a high risk of VTE. LMWH was not effective in any of the risk groups for prevention of VTE. Low- and high risk individuals can be identified by using the L-TRiP(cast) score which showed good validation performance. Nevertheless, the best treatment strategy for these patients is yet to be determined.

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