Thrombosis prophylaxis after knee arthroscopy or during lower leg cast immobilization : determining the balance between benefits and risks

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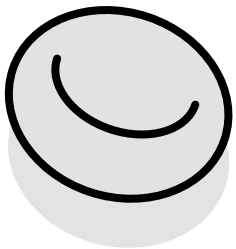
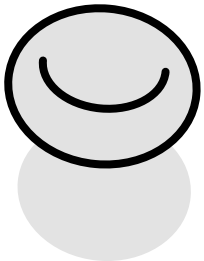
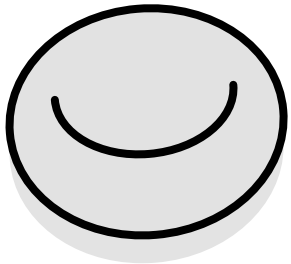
CHAPTER

Prevention of venous thromboembolism during lower leg cast immobilization: a randomized controlled trial







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Abstract

Background

Patients who need lower leg cast immobilization have an increased risk for developing venous thromboembolism. From previous trials that studied the efficacy of anticoagulant therapy an overall risk-benefit balance could not be established. Therefore, guidelines have been reluctant to recommend anticoagulant treatment.

Methods

We conducted a pragmatic, multicenter, randomized, controlled, open label, blinded endpoint trial in which patients with lower leg cast immobilization, with or without surgery, were randomly assigned to receive either low-molecular-weight-heparin (LMWH), 2850 IU (or 5700 IU in patients >100 kilograms) once daily, for the entire immobilization period, or no therapy. The primary outcome was the occurrence of symptomatic venous thromboembolism within three months following lower leg cast immobilization and the primary safety outcome was the occurrence of major bleeding within this time frame.

Results

1519 patients were enrolled, of whom 761 were randomly assigned to LMWH and 758 to no treatment. 1435 patients were included in the intention-to-treat analysis. A venous thromboembolic event occurred in 10/719 (1.4%) patients in the LMWH group and in 13/716 (1.8%) patients in the no therapy group, for a relative risk with LMWH of 0.8; 95% confidence interval (CI) 0.3 to 1.7; (risk difference -0.4%; 95% CI –1.7 to 0.9). No major bleeding event occurred.

Conclusion

In patients with lower leg cast immobilization, with or without additional surgery, thromboprophylaxis with daily LMWH during immobilization was not effective for the prevention of symptomatic venous thromboembolism. These results do not support routine thromboprophylaxis in these patients.

Introduction

Patients who are treated with lower leg cast immobilization have an increased risk for developing venous thromboembolism (VTE) (i.e. deep vein thrombosis [DVT] or pulmonary embolism [PE]).[1] Such patients therefore often receive anticoagulant therapy to prevent this. However, the magnitude of the risk for VTE following cast immobilization has not been reliably estimated (varies in studies between 0% and 5.5%)[2-5] and it is unknown whether the risks of major bleeding outweigh the benefits of treatment. In a Cochrane review, six small trials have been summarized in an attempt to answer the question if anticoagulant therapy is effective in these patients.[6] Most of these trials studied the occurrence of asymptomatic thrombosis as primary outcome in order to reduce the required sample size, and were therefore underpowered to draw conclusions on the prevention of symptomatic events. An overall risk-benefit balance could not be established and therefore international guidelines have been reluctant to advise in favor or against anticoagulant treatment in these patients.[7]

The Prevention Of Thrombosis after CAST Immobilization [POT-CAST] trial was therefore set up to compare anticoagulant treatment (Low Molecular Weight Heparin [LMWH]) with no therapy for the prevention of symptomatic VTE in patients treated with lower leg cast immobilization. We hypothesized that treatment with anticoagulants during the complete period of cast immobilization was effective for the prevention of symptomatic VTE and that this benefit outweighed the bleeding risk.

Methods

Study oversight and design

The POT-CAST trial is a prospective, multicenter, randomized, controlled, open label, blinded endpoint trial comparing two treatment strategies, i.e., one by which the anticoagulant LMWH is administered during immobilization versus one by which it is not, in patients treated with lower leg cast immobilization. The POT-CAST study was designed as a pragmatic trial to achieve maximal generalizability. The trial protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center; no methodological changes were made after approval. The POT-CAST trial was funded by The Netherlands Organization for Health Research and Development (project number 171102001) which had no role in the study design, analysis or preparation of the manuscript. The trial was registered at clinicaltrials.gov, number: NCT01542762. All

authors of the study group vouch for the accuracy and completeness of the reported data.

Participants

The POT-CAST trial was performed in eight hospitals in the Netherlands (seven teaching hospitals and one tertiary academic medical center, listed in the Supplementary Appendix). All patients, aged 18 years or older, presenting at the emergency department, who were treated with lower leg cast immobilization (no polytrauma) for at least one week were eligible for inclusion. Patients who underwent surgery of the lower leg before or after cast immobilization were also included. Exclusion criteria were a history of VTE, contra-indication for the use of LMWH (e.g. recent major bleeding), pregnancy and another indication for current use of anticoagulant therapy (either LMWH, vitamin K antagonists or direct oral anticoagulants) such as atrial fibrillation. Furthermore, patients with insufficient knowledge of the Dutch language, mental or physical disability to fulfil study requirements and patients who had already participated in the trial (for a previous cast) were excluded. All participants provided written informed consent.

Study procedures and intervention

Eligible patients were randomly assigned to receive either no treatment or a prophylactic dosage of LMWH (type of LMWH according to the hospitals preference, i.e. nadroparin or daltparin) once daily for the entire period of immobilization. The first dose was administered at the emergency department after randomization. Nadroparin 2850 IU subcutaneous or dalteparin 2500 IU subcutaneous was used for patients weighing less than 100kg, whereas patients over 100kg received a double dose.

Patients received an information leaflet for signs and symptoms of VTE and were advised to seek medical care if such symptoms arose. Follow-up started from the day of cast application for a period of 3 months as the risk for VTE returns to baseline after this period.[8] In addition to regular hospital visits, digital (online) or postal questionnaires on study compliance (e.g. duration of plaster cast), study outcomes, and study medication adherence were sent 3 and 7 weeks after cast application. In addition, patients were requested to complete a questionnaire on risk factors for VTE and hemorrhage. Finally, all patients were contacted by telephone after 3 months and asked whether any study outcome had occurred, i.e., if they had undergone examination for a suspected VTE, whether any hospital visits had taken place and whether they had adhered to

the assigned treatment. In case of no response, patients' general practitioners were contacted to determine if any study outcome or death had occurred. For all unresponsive patients the vital status was acquired from the Dutch population register. Detailed information on study outcomes was collected from patients' electronic hospital files and radiology reports. Data were centrally collected in a web-based database management system.[9]

Randomization and blinding

Eligible patients were randomly allocated to the study arms in a 1:1 ratio. Randomization was carried out centrally (online using Promise[9]) by the treating physician. To ensure concealment of treatment allocation the treating physicians were unaware of the allocation scheme and block sizes. Randomization was stratified by study center and by conservative or operative treatment (which was assessed at randomization). Patients and caregivers were not blinded for the allocated treatment.

Study outcomes

The primary outcome was the occurrence of symptomatic venous thromboembolism, i.e. deep vein thrombosis, or pulmonary embolism. The primary safety outcome was the incidence of major bleeding within the same time period.[10] Clinically relevant non-major bleeds (CRNMB) were considered as a secondary outcome (related to contact with a physician) and all other bleeds were registered as minor. All possible outcomes were evaluated and assessed by a blinded and independent outcome adjudication committee. All outcome definitions can be found in the Supplementary Appendix.

Sample size

We assumed an incidence of VTE in the absence of treatment of 2% as the basis of our sample size calculations. Based on a risk reduction of 85%[11], we calculated a necessary sample size of 625 subjects in each arm (alpha 0.05, power 80%, two-sided). To account for a maximum drop-out rate of 15%, we aimed to include 750 patients in each study arm. For our primary safety outcome, we assumed a risk of major bleeding of 0.3% which allowed us to determine an upper limit of the 95%CI of about 1%.[1,12,13]

Safety monitoring

A pre-specified interim analysis for safety purposes was planned and reviewed by an independent data safety monitoring board (DSMB) after 50% and 75% of the targeted

number of patients were included. If at interim analysis the intervention would prove to be clearly contraindicated by means of an increased risk of major bleeding (upper limit of the 95%Confidence Interval (CI) >1%), we considered to terminate the study prematurely. Furthermore, the DSMB provided advice on the conduct of the trial to the steering committee.

Statistical analysis

All analyses followed the pre-specified plan as described in the study protocol. Baseline characteristics were summarized as means with standard deviations (SD) or proportions as appropriate. Data on outcome events were analyzed by the intention-to-treat principle, excluding patients who were inadvertently randomized since they had not met in-or exclusion criteria. For the primary outcome, cumulative incidences with 95% Confidence Intervals (CI), based on the binomial distribution in both groups for symptomatic VTE were estimated and compared by means of relative risks (RR) and risk differences (RD) with their 95%CIs. Similar analyses were performed for the safety outcomes. In a per-protocol analysis we included only those individuals who had adhered to the study protocol. Analyses were performed in IBM SPSS Statistics for Windows, version 23 and in Stata, version 14 SE.

Results

Study population

From March 2012 through January 2016, 1519 patients were enrolled at eight study centers (Figure 1). 761 were randomly assigned to LMWH and 758 patients to no treatment. After randomization, 33 patients were excluded because the original in- or exclusion criteria had not been met (e.g. VTE in patient history, no cast); 14 in the LMWH group versus 19 in the no treatment group. Of the remaining patients a total of 23 withdrew consent and 28 were lost to follow-up, leading to 719 patients in the LMWH and 716 in the no treatment group who were included in the intention-to-treat analysis. Patient characteristics were well balanced across both groups. Overall, 49.9% of patients were men and mean age was 46.5 (SD16.5) years (Table 1). The majority of patients (1279, 89%) were treated with cast immobilization because of a fracture (Table 2). Among all patients with a fracture, 530 (41%) had one or more broken metatarsal bones and 492 (38%) had an ankle fracture. Surgery was performed in 170 patients as part of their treatment and 105 patients had multiple fractures.

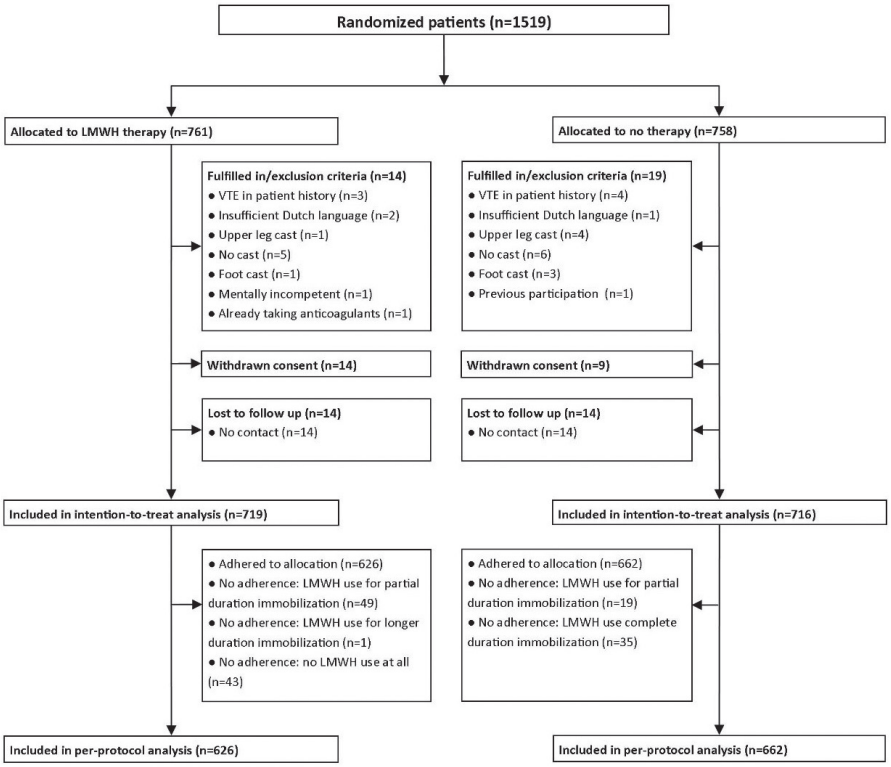

Figure 1. *Flow chart of patients*

Figure legend: Flow chart of patients enrolled, randomized and included in the intention to treat and per-protocol analysis.

Table 1. *Characteristics of study population*

Patient characteristics §	**LMWH* (n=719)**	**No treatment (n=716)**
Male sex, n (%)	347 (48.3)	369 (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, n (%)		
Current	173 (26.1)	178 (26.8)
Ever	188 (28.4)	178 (24.9)
Oral contraceptives use, n (% of women)	86 (24.7)	69 (21.2)
Paid employment (%)	442 (66.6)	469 (65.5)
Cancer		
Within last year	8 (1.2)	9 (1.3)
More than 1 year ago	26 (3.9)	20 (3.0)
Family history of venous thromboembolism, n (%)	60 (10.6)	52 (9.4)

§ Percentages of complete data, data were missing for the following characteristics: BMI in 112 patients, Smoking in 107 patients, Oral contraceptives use in 45 patients, Paid employment in 102 patients, Cancer in 87 patients, Family history of venous thromboembolism 316 patients.

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† BMI: body mass index in kilogram divided by the square of the height in meters.

Table 2. *Lower leg cast details*

Lower leg cast details §¶	**LMWH* (n=719)**	**No treatment (n=716)**
Duration cast in weeks, mean (SD)	4.9 (2.5)	4.9 (2.5)
Lower leg cast indication, n (%)		
Fracture	648 (90.1)	631 (88.1)
Achilles tendon rupture	40 (5.6)	54 (7.5)
Ankle distortion	18 (2.5)	17 (2.4)
Antalgic	6 (0.8)	3 (0.4)
Contusion	5 (0.7)	8 (1.1)
Other	2 (0.3)	3 (0.4)

Table 2. *Lower leg cast details (continued)*

Lower leg cast details §¶	**LMWH* (n=719)**	**No treatment (n=716)**
Fracture type, n(%)		
Ankle	253 (39.0)	239 (37.9)
44-A type	60 (28.3)	44 (22.1)
44-B type	125 (57.5)	129 (64.8)
44-C type	27 (12.7)	26 (13.1)
Other†	16 (7.5)	15 (7.5)
Metatarsal	276 (42.6)	254 (40.3)
Calcaneus	31 (4.8)	25 (4.0)
Pilon tibial	2 (0.3)	1 (0.2)
Tibia and fibula shaft	1 (0.2)	2 (0.3)
Talus	21 (3.2)	29 (4.6)
Tarsal	42 (6.5)	56 (8.9)
Phalanx	11 (1.7)	12 (1.9)
Lisfranc	4 (0.6)	2 (0.3)
Maisonneuve	2 (0.3)	3 (0.5)
Other	5 (0.8)	8 (1.3)
Multiple fractures, n (%)	53 (8.4)	52 (8.4)
Surgery, n (%)	91 (12.7)	79 (11.0)
Total duration operation in minutes, mean (SD)	75.2 (32.2)	78.5 (27.4)
Duration surgery in minutes, mean (SD)	50.2 (28.2)	50.9 (21.7)

§ Percentages of complete date, data were missing for the following characteristics: AO classification ankle fracture type in 50 patients, duration operation or surgery in 33 patients

¶ SD denotes Standard Deviation

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† Fractures not meeting criteria to be classified in either type.

Effectiveness

In the LMWH group, 10/719 patients developed a VTE (6 DVTs, 3 PEs and 1 patient had both) for a cumulative incidence of 1.4% (95%CI 0.7 to 2.5) (Table 3). In the no treatment group, 13/716 developed a VTE (8 DVTs, 4 PEs and 1 patient developed both), for a cumulative incidence of 1.8% (95%CI 1.0 to 3.1). The RR for VTE following lower leg cast with LMWH therapy versus no treatment was 0.8 (95%CI 0.3 to 1.7) with a RD of -0.4% (95%CI -1.7 to 0.9). Additionally, one patient in each group developed a distal superficial vein thrombosis (which was not considered as an outcome event). The Supplementary Appendix shows all DVT and PE locations.

The study protocol was followed by 626/719 (87%) patients in the LMWH group and by 662/716 (92%) in the no treatment group (Figure 1). A VTE occurred in 10/626 patients in the LMWH group and in 12/662 patients in the no treatment group following a per-protocol analysis (Table 4). The cumulative incidence for VTE was 1.6% versus 1.8%, respectively, for an RR of 0.9 (95%CI 0.4 to 2.0). The 13th patient who developed VTE (assigned to no treatment), had used Nadroparin for 4 weeks after surgery (on this patient's own initiative).

Table 3. *Primary efficacy outcomes, Intention-to-treat analysis†*

Outcome	LMWH*(n=719), no. (%; 95%CI)	No treatment (n=716), no. (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	6 (0.8; 0.3 to 1.8)	8 (1.1; 0.5 to 2.2)	0.7 (0.3 to 2.1)	-0.3 (-1.3 to 0.7)
PE	3 (0.4; 0.1 to 1.2)	4 (0.6; 0.2 to 1.4)	0.7 (0.2 to 3.3)	-0.1 (-0.9 to 0.6)
DVT and PE	1 (0.1; 0.0 to 0.8)	1 (0.1; 0.0 to 0.8)	1.0 (0.1 to 15.9)	0.0 (-0.4 to 0.4)
Total	10 (1.4; 0.7 to 2.5)	13 (1.8; 1.0 to 3.1)	0.8 (0.3 to 1.7)	-0.4 (-1.7 to 0.9)
Primary safety outcome				
Major Bleed	0 (0; 0 to 0.5)	0 (0; 0 to 0.5)	-	-
Secondary safety outcome				
CLNMB Bleed	1 (0.1; 0.0 to 0.8)	0 (0; 0 to 0.5)	-	0.1 (-0.1 to 0.4)

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference, CLNMB, denotes clinically relevant non-major bleeding

Table 4. *Primary efficacy outcomes, Per-protocol analysis†*

Outcome	LMWH*(n=626), n (%; 95%CI)	No treatment (n=662), n (%; 95%CI)	RR (95%CI)	RD (95%CI), percentage points
Primary efficacy outcome				
DVT	6 (1.0; 0.4 to 2.1)	7 (1.1; 0.4 to 2.2)	0.9 (0.3 to 2.7)	-0.1 (-1.2 to 1.0)
PE	3 (0.5; 0.1 to 1.4)	4 (0.6; 0.2 to 1.5)	0.8 (0.2 to 3.5)	-0.1 (-0.9 to 0.7)
DVT and PE	1 (0.2; 0.0 to 0.9)	1 (0.2; 0.0 to 0.8)	1.1 (0.1 to 16.9)	-0.0 (-0.4 to 0.4)
Total	10 (1.6; 0.8 to 2.9)	12 (1.8; 0.9 to 3.1)	0.9 (0.4 to 2.0)	-0.2 (-1.6 to 1.2)
Primary safety outcome				
Major Bleed	0 (0; 0 to 0.6)	0 (0; 0 to 0.6)	-	-
Secondary safety outcome				
CLNMB Bleed	1 (0.1; 0.0 to 0.9)	0 (0; 0 to 0.6)	-	0.2 (-0.2 to 0.5)

† DVT denotes Deep Vein Thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference, CLNMB, denotes clinically relevant non-major bleeding

** Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

Safety outcome

During the 3-month follow-up period one CRNMB occurred in 1/719 (0.14%) patients in the LMWH group as compared with none in the no treatment group, while no major bleedings occurred. A minor bleeding was found in 56/719 (7.8%) and in 49/716 (6.8%) patients in the LMWH and no treatment group, respectively (Supplementary appendix). One patient assigned to no therapy died within 3 months after randomization, which death was assessed by the outcome adjudication committee as possibly due to pulmonary embolism. However, because no autopsy was performed and the patient was aged >90 years and suffered from heart failure, a conclusive diagnosis could not be made. The Supplementary appendix provides a sensitivity analysis including this possible event in the intention-to-treat analysis, which did not essentially change the main result. No deaths occurred among any of the patients who were lost to follow up.

Discussion

In the POT-CAST trial we investigated the effectiveness of thromboprophylaxis versus no treatment for the prevention of VTE in patients with lower leg cast immobilization. We found that treatment with anticoagulants during the complete period of cast immobilization was not effective for the prevention of VTE.

Previous findings from six small trials (totaling 1536 patients) are in contrast with ours with a pooled odds ratio of 0.49 (95%CI 0.34-0.72) and 0.16 (95%CI 0.05 to 0.56) (only in four trials) in favor of LMWH treatment for the prevention of asymptomatic (DVT only) and symptomatic VTE, respectively.[6] Nevertheless, in addition to not being individually powered for symptomatic events, these trials suffered from severe methodological weaknesses, such as an overall loss to follow up of 32%.[2] Furthermore, most trials included only patients with high risk for VTE, e.g., only patients undergoing surgery[4] or only patients with a duration of cast immobilization of more than five weeks.[5] For these reasons, the ACCP guidelines currently refrain from advising in favor of thromboprophylaxis in patients with lower leg cast immobilization.[7]

Strengths of the POT-CAST trial are first the pragmatic design: participants formed a nonselected, wide variety of patients in need of lower leg cast immobilization, and no restrictions were made regarding cast duration (apart from an expected treatment of at least one week). The exclusion criteria were minimal, hence maximizing generalizability towards the clinic. Also, although the study design was open, a blinded outcome adjudication committee classified all events. Finally, we had almost no loss to follow-up (2%) and only a limited number of patients withdrew consent (1%).

Potential limitations that may explain the minimal effect are first the open design which theoretically could have led to differential contacting of a physician in case of signs and symptoms of VTE, which may have occurred as VTE was suspected 17 vs 25 times in the LMWH and no treatment group, respectively. Nevertheless, the diagnosis was confirmed at the same rate in both groups, so even though the suspicion rate may have differed, this did not lead to bias: 10 (59%) vs 13 (52%) patients in the LMWH and no treatment group, respectively. It should be noted that we intentionally chose for non-blinding to reflect general practice, where in 'real life' patients may also contact their doctor differently depending on their type of treatment. Second, treatment adherence was not 100%, though good (and monitored three times during three months); 87%

of patients allocated to LMWH adhered to this treatment as compared with 92% in the group allocated to no treatment. Furthermore, out of the 93 patients who did not adhere to LMWH, 49 adhered at least partially (prophylactic treatment was most often stopped because patients were mobile or changed to a less rigid cast, e.g. foot cast). Again, these figures represent daily life situations and it is not to be expected adherence would be better outside a trial context (a previous large prospective study in 4388 orthopedic surgery patients showed an identical adherence rate of 87%)[14] Moreover, the per protocol analyses showed similar results as the intention-to-treat analysis. Lastly, the absence of effect may have been due to the duration, dose, or type of anticoagulant treatment. For example, 9/23 patients developed VTE after their cast was removed, of whom 6 had been treated with LMWH. This might indicate a need for extended prophylactic treatment, possibly in high-risk groups only: It can be hypothesized that patients who develop symptomatic VTE under treatment have a high baseline risk, where cast application is a relatively small trigger, added to the baseline risk and leading to thrombosis.[15] In such individuals their high risk cannot be sufficiently lowered with a prophylactic dose of anticoagulant treatment. We demonstrated in another dataset that patients who developed VTE after plaster cast immobilization were found to have (several) other risk factors for VTE.[8] In the current trial, other risk factors were indeed present in the patients who developed VTE under treatment, e.g. high age, male sex, hormone use, family history of VTE. A similar situation is possibly present in patients with hip replacement where 2% of patients still develop VTE despite anticoagulant prophylaxis.[16] We therefore speculate that for these 'doomed' individuals the routine prophylactic dose is not sufficient. Nevertheless, exposing all patients with plaster cast to a more intense anticoagulant scheme is not feasible considering the numbers needed to treat and harm. Risk prediction, identification of high-risk groups (which we previously showed to be feasible[17]) and targeted treatment should therefore be the topic for further research in this patient group.

In conclusion, in the POT-CAST trial we found that for patients requiring lower leg cast immobilization, anticoagulant medication was not superior to no therapy for the prevention of symptomatic VTE. In addition, no critical safety issues regarding treatment were found, leading to an overall neutral risk-benefit ratio for anticoagulant therapy. Clinicians should not routinely prescribe thromboprophylaxis in patients treated with lower leg cast immobilization.

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Supplementary appendix

Participating study centers (all located in the Netherlands)

Alrijne Hospital, Leiderdorp
Groene Hart Hospital, Gouda
Haga Hospital, The Hague
Isala Hospital, Zwolle
Medical Center Haaglanden Hospital, The Hague
Leiden University Medical Center, Leiden
Reinier de Graaf Hospital, Delft

Primary and Secondary Outcome definitions

Primary study outcomes

The primary efficacy outcome is symptomatic venous thrombosis, i.e., deep venous thrombosis (DVT) or fatal or non-fatal pulmonary embolism (PE).

The following definitions are applied to confirm a suspected episode of symptomatic PE/DVT:

1. DVT: abnormal compression ultrasound
2. PE: an intraluminal filling defect in segmental or more proximal branches on spiral CT scan or a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or detected at autopsy.

The primary safety outcome is major bleeding, defined according to the guidelines of the ISTH[1]:

a) fatal bleeding, or
b) symptomatic bleeding in a critical area or organ, or
c) extra surgical site bleeding causing a fall in hemoglobin level of 1.24 mmol/L (2.0 g/dl) or more, or leading to transfusion of one or more units of whole blood or red cells, or
d) surgical site bleeding that requires a second intervention or a hemarthrosis interfering with rehabilitation, or surgical site bleeding that needs blood transfusion.

Secondary study outcomes

Other clinically relevant bleeding, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.

[1] Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8(1):202-204.

***Table** - Location of thrombotic event*

Location thrombotic event	LMWH Total no.	No Treatment Total no.	Total no.
Pulmonary embolism*			
Peripheral	1	1	2
Central	0	1	1
Multiple	3	3	6
Deep vein thrombosis*			
Proximal	5	3	8
Distal	2	6	8

**Two patients had both deep vein thrombosis and pulmonary embolism*

Table. *List of bleeding events*

Bleeding type	**LMWH Total no.**	**No therapy Total no.**
Major bleeding †	0	0
Total	**0**	**0**
Clinically relevant bleeding ‡		
Hematuria	1	0
Total	**1**	**0**
Minor bleeding §		
Rectal bleeding	1	2
Menstruation (heavier than normal)	1	0
Throat	1	0
Abdomen (skin)	1	0
Arms, legs	2	2
Nose bleeding §	33	27
Hematoma >3cm §	17	18
Spontaneous hematoma >3cm*	9	11
Hematoma on other place than arms or legs >3cm*	8	2
Grand Total ¶	**56**	**49**

† *defined according to the ISTH guidelines (JTH 2010;8:202-4)*

‡ *defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.*

§ *defined as other bleeding not meeting the criteria for major or clinically relevant bleeding, no contact with a physician.*

**does not add up as patients could have both conditions.*

¶ *total minor bleedings (minor bleeding and nose bleeding and hematoma>3cm)*

Sensitivity analysis

One patient assigned to no treatment died within 3 months after randomization, which death was assessed by the outcome adjudication committee as possibly due to pulmonary embolism. However, because no autopsy was performed and the patient was aged >90 years and suffered from heart failure, a conclusive diagnosis could not be drawn. This possible pulmonary embolism is added to the analysis shown below. The main results did not show an essential change (RR 0.7, 95%CI 0.3 to 1.6).

Table. *Sensitivity analysis – changes indicated in bold*

Outcome†	**LMWH*(n=719), no. (%; 95%CI)**	**No treatment (n=716), no. (%; 95%CI)**	**RR (95%CI)**	**RD (95%CI), percentage points**
Primary efficacy outcome				
DVT	6 (0.8; 0.3 to 1.8)	8 (1.1; 0.5 to 2.2)		-0.3 (-1.5 to 0.8)
PE	3 (0.4; 010 to 1.2)	**5 (0.7; 0.2 to 1.6)**		-0.3 (-1.3 to 0.6)
DVT and PE	1 (0.1; 0.0 to 0.8)	1 (0.1; 0.0 to 0.8)		0.0 (-0.7 to 0.7)
Total	10 (1.4; 0.7 to 2.5)	**14 (2.0; 1.1 to 3.3)**	**0.7 (0.3 to 1.6)**	**-0.6 (-1.9 to 0.8)**
Primary safety outcome				
Major Bleeding	0 (0; 0 to 0.5)	0 (0; 0 to 0.5)	-	0.0 (-0.5 to 0.5)
Secondary safety outcome				
CLNMB Bleeding ‡	1 (0.1; 0.0 to 0.8)	0 (0; 0 to 0.5)	-	0.1 (-0.4 to 0.8)

† *DVT denotes deep vein thrombosis, PE denotes Pulmonary Embolism, CI denotes Confidence Interval, RR denotes Relative Risk, RD denotes Risk Difference*

***** *Low Molecular Weight Heparin, either Nadroparin or Dalteparin.*

‡ *CLNMB: clinically relevant non-major bleeding*