Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): a randomised controlled trial.

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Keywords
Thromboprophylaxis
Deep vein thrombosis
Venous thromboembolic event
Lower leg immobilisation
Fracture

Summary

Background The immobilisation of the lower leg is associated with deep vein thrombosis (DVT). However, thromboprophylaxis in patients with a below-knee plaster cast remains controversial. We examined the efficacy and safety of nadroparin and fondaparinux to ascertain the need for thromboprophylaxis in these patients.

Methods PROTECT was a randomised, controlled, single-blind, multicentre study that enrolled adults with an ankle or foot fracture who required immobilisation for a minimum of four weeks. The patients were randomly assigned (1:1:1) to a control group (no thromboprophylaxis) or to one of the intervention groups: daily subcutaneous self-injection of either nadroparin (2850 IE anti-Xa = 0·3 ml) or fondaparinux (2·5 mg = 0·5 ml). A venous duplex sonography was performed after the removal of the cast or earlier if thrombosis was suspected. The primary outcome was the relative risk of developing DVT in the control group compared with that in both intervention groups. This trial is registered at ClinicalTrials.gov, number NCT00881088.

Results Between April 2009 and December 2015, 467 patients were enrolled and assigned to either the nadroparin group (n=154), the fondaparinux group (n=157), or the control group (n=156). A total of 273 patients (92, 92, and 94 patients, respectively) were analysed. The incidence of DVT in the nadroparin group was 2/92 (2·2%) compared with 11/94 (11·7%) in the control group, with a relative risk of 5.4 (95% CI 1·2 – 23·6; p = 0·011). The incidence of DVT in the fondaparinux group was 1/92 (1·1%), yielding a relative risk of 10·8 (95% CI 1·4 – 80·7; p = 0·003) compared with that in the control group. No major complications occurred in any group.

Conclusion Thromboprophylaxis with nadroparin or fondaparinux significantly reduces the risk of DVT in patients with an ankle or foot fracture who were treated in a below-knee cast without any major adverse events.

Keywords

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Introduction

Deep vein thrombosis (DVT) is a well-recognised complication after trauma and subsequent immobilisation. However, for several injuries, no consensus exists on the way to prevent this complication or even on the need to prevent it.[1] In particular, the prophylaxis of venous thromboembolism (VTE) in patients who are treated conservatively in a below-knee plaster cast is controversial; therefore, there is large variation in whether to prescribe pharmacological thromboprophylaxis in daily clinical practice.[2–4]

The incidence of DVT in patients with a below-knee plaster cast without thromboprophylaxis ranges from 4% to 19%.[5–10] Although meta-analyses suggest that thromboprophylaxis significantly reduces the risk of DVT,[11,12] most guidelines advise against the routine use of pharmacological prophylaxis in these patients because of the lack of sufficient evidence, also debating the clinical significance of asymptomatic DVT and the cost-effectiveness of thromboprophylaxis.[13–15]

Previous randomised controlled studies have assessed the use of low-molecular-weight heparins after leg injury; however, no clear distinction was made among fractures and rupture of the Achilles tendon, operative and conservative treatment, and above- or below-knee plaster casts.[7–10,16,17] All of these variables are possible confounders of the results.

The objective of this multicentre randomised controlled trial was to assess the incidence of DVT in patients with a conservatively treated fracture of the ankle or foot immobilised in a below-knee plaster cast and to evaluate the efficacy and safety of subcutaneously administered low-molecular-weight heparin (LMWH) nadroparin and synthetic factor-Xa-inhibitor fondaparinux.

Methods

Study design

A prospective, randomised, controlled, single-blind, multicentre study was performed between April 2009 and December 2015 in seven Dutch hospitals (the participating investigators are listed in the Appendix). All study documents and procedures were approved by the appropriate institutional review boards and ethics committees at each study site, and the study was performed according to the principles of the Declaration of Helsinki. All patients received written and verbal information about the trial, and written consent was obtained from each participant. The study protocol is available at http://www.protectstudie.nl/html/studyProtocol.html. This trial was registered at clinicaltrials.gov, number NCT00881088.

Patients

We enrolled adults (≥18 years) diagnosed with a fracture of the ankle or foot who required non-surgical treatment with immobilisation in a below-knee plaster cast for a minimum of four weeks. The exclusion criteria included the following: a delay between injury and the emergency department (ED) visit of more than 72 hours; a known hypersensitivity to nadroparin or fondaparinux; a history of venous thromboembolism; patients who were already on continuous anticoagulant therapy; hypercoagulability; a bleeding tendency/disorder; pregnancy or lactation; ‘active’ malignancy; a severe hepatic or renal impairment (deficiency of clotting factors or creatinine clearance < 30 ml/min); retinopathy; previous or active bleeding from the digestive tract; a haemorrhagic stroke within the previous two months; a major surgery within the previous two months; an intraocular/spinal/brain surgery within the previous year; and severe hypertension (systolic blood pressure above 180 mmHg or diastolic blood pressure above 110 mmHg).

The following risk factors for DVT were recorded: age, sex, body-mass index (BMI), current smoking, use of oestrogen-containing hormonal replacement therapy, oral contraception and varicose veins.

Randomisation and masking

After meeting the aforementioned inclusion criteria and obtaining informed consent, patients were enrolled and randomly assigned (by use of sealed, numbered envelopes in a ratio of 1:1:1 in blocks of 15, stratified according to centre) to one of the three study groups by the treating physician at the ED. The treating physician at the ED was not involved in the remainder of the trial.

The ultrasound technician who assessed the primary outcome was blinded to the treatment.

Procedures

The participants in the intervention groups were instructed by a trained nurse to subcutaneously self-inject either nadroparin (2850 IE anti-Xa = 0·3 ml, given once daily) or fondaparinux (2·5 mg = 0·5 ml, given once daily). These dosages are standard for the use in thromboprophylaxis. The participants were given pre-filled disposable syringes for once-daily administration during the duration of the immobilisation.

The participants received a letter that explained the clinical symptoms associated with the possible development of DVT, pulmonary embolism (PE) and side effects of the medication and were asked to contact the ED if any of these occurred. Any signs of VTE or side effects were evaluated by the physician who was present at the removal of the cast and documented on the case report form.

By counting the number of used syringes at the end of the study period and by asking the patient how many injections they had missed, we assessed the participants' compliance with the study.

A venous duplex sonography of the affected leg was performed after removal of the cast on the final day of medication administration or earlier if thrombosis was suspected.

The duplex sonography was performed by experienced technicians according to a strict diagnostic test protocol that systematically assessed the veins of the lower extremity (Appendix 1). When a vein was incompressible or lacked flow, a diagnosis of DVT was made.

In the case of a suspected pulmonary embolism, a CT angiography of the lungs was performed.

Outcomes

Efficacy (primary endpoint) was assessed by the percentage of patients in each intervention group who had developed a DVT verified by duplex sonography and/or a symptomatic pulmonary embolism verified by CT angiography compared with those of the control group.

Safety (secondary endpoint) was measured by recording adverse events, such as major bleeding, injection site haematomas and other minor bleedings, and allergic reactions.

Statistical analysis and data management

The sample size calculation yielded a necessary 223 patients in each group (sample size 669 in total) of the study to detect a reduction in the cumulative incidence of DVT from 10% in the control group (based on available literature) to 4% in the intervention groups, assuming a power of 80% and a one-sided significance level of 0·05. The number needed to treat was 17. The dropout rate was estimated to be 15%; thus, the number of subjects to be included was 770.

The primary analysis was performed according to the intention-to-treat principle. Patients who received at least one dose of the study medication were included in the analyses of efficacy and safety if a venous duplex sonography was obtained.

A comparison was made between each intervention group and the control group. The primary and secondary outcome measures were analysed using a chi-square test or Fisher's exact test for dichotomous variables and Student's T-test for continuous variables. A p-value less than 0·05 was considered statistically significant in all tests. The data were analysed using SPSS statistical software (version 22.0.0.0). The study design, data entry, editing, and analyses were all carried out by the authors.

Role of the funding source

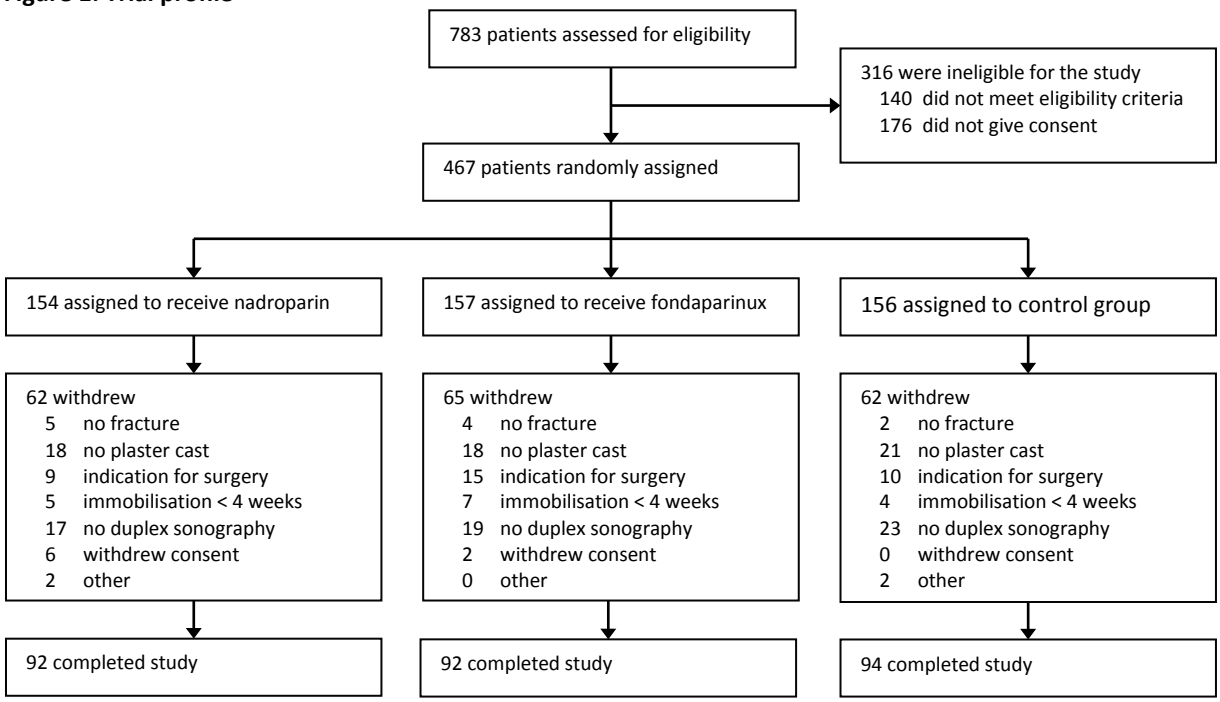
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All the authors had full access to all of the data and were responsible for the decision to submit for publication.

Results

From April 1st, 2009 to December 31th, 2015, 783 patients were assessed for eligibility; 316 were ineligible for the study. After this period, we stopped the patient recruitment because there were formal stopping rules regarding the duration of the study and the scheduled date of closure that were agreed upon by the review boards and ethics committees.

Among the 467 patients enrolled, 154 were randomly assigned to receive nadroparin, 157 to receive fondaparinux and 156 to the control group. A total of 189 patients were lost to follow up in the efficacy analysis (Figure 1) because at the reassessment after one week no fracture was diagnosed, there were indications for surgical treatment or the patients were treated without a below-knee plaster cast for the duration of four weeks; thus, these patients fell outside the inclusion criteria or no duplex sonography was performed and the primary outcome could not be analysed. Two patients in the nadroparin group stopped because of an allergic reaction and no ultrasound was performed. In the control group, two patients were excluded during the study period; one was excluded because of a diagnosis of malignancy and the other because of surgery for an aneurysm of the abdominal aorta. Thus, 273 patients (94 in the control group, 92 in the nadroparin group and 92 in the fondaparinux group) were included in the intention-to-treat analysis.

Figure 1: Trial profile



The baseline characteristics and risk factors for vascular disease were similar in all three groups (Table 1).

Table 1: Baseline characteristics of the intention-to-treat population

Characteristics	Control	Nadroparin	Fondaparinux

	(n = 94)	(n = 92)	(n = 92)
Age (years)	44·5 (17·2)	47·7 (16·4)	49·7 (17·3)
Male sex	38 (40%)	39 (42%)	41 (45%)
Body-mass index	25·1 (3·8)	26·4 (4·5)	26·5 (4·1)
Current smoking	29 (33%)	28 (32%)	18 (21%)
Current hormone therapy	8 (9%)	4 (5%)	6 (7%)
Varicose veins	14 (16%)	6 (6·8%)	16 (19%)
Duration of immobilisation (days)	40·3 (8·6)	40·2 (8·5)	38·0 (8·7)
Data are mean (SD) or n (%).			

Compliance with the study treatment was close to 100% in both groups (data not shown).

No major complications (bleeding, infection of the injection location, cutaneous necrosis) occurred in any group. A total of 31 patients with minor complications were from the intervention groups: 26 (19 (27·1%) in the nadroparin and 7 (9·6%) in the fondaparinux group) reported small haematomas, two (one in each intervention group (1·4%)) considered the injections to be painful, two (one in each intervention group (1·4%)) reported haematuria and one patient (1·4%) in the nadroparin group reported dark stools.

Deep vein thrombosis was diagnosed in 11 of the patients who were randomly assigned to the control group (11·7%), in two of those assigned to receive nadroparin (2·2%) and in one of those assigned to receive fondaparinux (1·1%). Two patients with DVT in the control group presented with symptoms of pulmonary embolism before the removal of the cast, which was confirmed by CT angiography. None of the remaining DVT patients had developed symptoms of a venous thromboembolic event; thus, those DVTs were asymptomatic.

Table 2: Nadroparin vs control

	Control (n = 94)	Nadroparin (n = 92)	P-value*
DVT – no. (%)	11 (11·7)	2 (2·2)	0·011
* The P-value was calculated with the use of the Pearson Chi-Square test, 2-sided significance			

The analysis showed that the incidence of DVT in the group of patients treated with nadroparin was 2/92 (2·2%) compared with 11/94 (11·7%) in the control group, with a relative risk of 5·4 (95% CI 1·2 – 23·6; p = 0·011) (Table 2). The analysis of the group of patients treated with fondaparinux showed that the incidence of DVT was 1/92 (1·1%) compared with 11/94 (11·7%) in the control group, with a relative risk of 10·8 (95% CI 1·4 – 80·7; p = 0·003) (Table 3).

Table 3: Fondaparinux vs control

	Control (n = 94)	Fondaparinux (n = 92)	P-value*
DVT – no. (%)	11 (11·7)	1 (1·1)	0·003
* The P-value was calculated with the use of the Pearson Chi-Square test, 2-sided significance			

Discussion

This randomised controlled trial compared nadroparin or fondaparinux thromboprophylaxis in foot or ankle fracture patients who had been immobilised in a below-knee plaster cast for at least four weeks with a control group that did not receive any form of thromboprophylaxis. We found an 11·7% incidence of deep vein thrombosis diagnosed with venous duplex sonography in the control group. The incidence was significantly lower in patients who received daily subcutaneous injections of nadroparin or fondaparinux (2·2% and 1·1%,

respectively) during the complete period of immobilisation (p = 0·011 and p = 0·003). Two clinically significant PEs occurred in the control group, and the other DVTs were asymptomatic.

Previous comparative studies have shown that prophylaxis with LMWH in patients immobilised with a plaster cast can reduce the incidence of (asymptomatic) DVT to a greater or lesser extent. As an exception, Jorgensen et al. found prophylaxis to be insufficiently effective in their study.[7] In an RCT of 253 patients, Kock et al. found the incidence of DVTs with prophylaxis (nadroparin) to be significantly lower than that in their control group.[8] Kujath et al. showed the same in another RCT of 339 patients.[9] This study, however, was not blinded to treatment. Lassen et al., in an RCT of 371 patients, showed a significant reduction in DVT with the use of LMWH (reviparin), but they included patients with leg fractures who underwent surgery, which is known to be an independent risk factor for the development of DVT.[10] All of these studies were based on a heterogeneous group of patients with various fractures and soft-tissue injuries who were treated with or without surgery and the use of different means of immobilisation.

The patient population in our study was well defined and consisted solely of patients with a non-surgical fracture that was treated in a below-knee plaster cast. We found that treatment with nadroparin or fondaparinux was safe. Apart from some small injection site haematomas, there were no cases of major bleeding in any of the groups. Compliance was excellent in our study. This suggests that prophylaxis with nadroparin or fondaparinux during the entire period of immobilisation is feasible, even though both prophylactic regimens comprised the need for subcutaneous administration.

Most DVTs in our study were asymptomatic, diagnosed by venous duplex sonography (except for the two cases of PE in the control group). The clinical significance of such thrombi is much debated.[18,19] Nevertheless, a thrombus is a symptom of the underlying disease process, hypercoagulopathy, which we believe should be treated. There is no doubt that failure to recognise post-traumatic DVT can lead to long-term damage in the form of post-thrombotic syndrome or pulmonary embolism.[20,21] A total of 50% of pulmonary embolisms are caused by asymptomatic DVTs, and even small thrombi in distal veins can progress to proximal veins and cause major complications.[22]

In this study, we used nadroparin and fondaparinux as a thromboprophylactic treatment and compared it with the control group. We chose to compare two different thromboprophylactic regimens with a control group; nadroparin was chosen because it is the most commonly used thromboprophylaxis in the Netherlands,[3] and fondaparinux was chosen because at the start of the study, there were several studies that suggested that fondaparinux was more effective in preventing DVT compared with LMWH without proposing the risk of heparin induced thrombocytopenia (HIT).[23–25]
We think that our results can be extrapolated to other the use of other LMWH for preventing VTE in patients treated with a below-knee cast, such as enoxaparin and dalteparin. Although there are no previous studies comparing different LMWH's for this indication, studies comparing LMWH's for thromboprophylaxis in critical ill patients show no differences in efficacy and safety.[26] If any differences between LWMH preparations do exist, the must be extremely small.
We decided to refrain from administering a placebo in the control group because the outcome measure was objective (DVT or PE diagnosed by venous duplex sonography or pulmonary CT angiography, respectively).

In this study, we used venous duplex sonography to diagnose DVT. Although venography is considered the gold standard in this setting,[27, 28] it is rarely used as a first-line investigation for DVT. It is an invasive procedure, and there is a reported incidence of serious adverse reactions to the contrast medium ranging from 0·4% to 2%.[29] Venous duplex sonography is the most common non-invasive test used to diagnose venous thrombosis of the extremities. Compared with venography, duplex ultrasound has been shown to be reliable in the diagnosis of proximal symptomatic DVT, with a sensitivity and specificity of over 90%. For distal DVTs, a sensitivity of 73% can be reached by combining compression ultrasound with colour Doppler ultrasound.[14,30] This may mean that

the incidence of asymptomatic DVT in our study is underestimated as we used ultrasound instead of venography to diagnose DVT. However, this underestimation would have affected all three of the study arms.

This study was prematurely terminated because of prior agreements with the review boards and ethics committees of the participating hospitals about the scheduled date of closure. No interim analyses were conducted. Unfortunately, we did not reach the sample size calculated by our power analysis during this period. Despite our efforts to enrol eligible patients, it proved difficult to obtain informed consent. In addition, a considerable number of patients were lost to follow up. This was mostly because many patients were excluded after one week when they failed to meet our inclusion criteria based on reassessment (they had no fracture, an indication for surgery was set, or they were not further treated with a below-knee plaster cast eg. soft-cast, etc.). The number of patients lost to follow up was divided equally among the three groups and will therefore not cause bias.

In conclusion, we found that thromboprophylaxis with nadroparin or fondaparinux significantly reduced the risk of a thromboembolic event in patients with a fracture of the ankle or foot who were conservatively treated with a below-knee cast without any major adverse events. We, therefore, propose to routinely prescribe thromboprophylaxis in these patients.

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Contributors
YMEG, RSB and RJD contributed to study design.
MMB and YMEG contributed to the literature search.
MMB, YMEG and the PROTECT study group contributed to data collection.
IBS contributed to data collection and data management.
MMB, WET and RJD did the statistical analysis of the data and the initial interpretation of the data.
MMB, YMEG and RJD wrote the first draft of the manuscript.
All authors contributed to final data interpretation and contributed to and approved the final draft of the manuscript.

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Declaration of interest

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Appendix 1: Test protocol venous duplex sonography

Objective

To detect or to rule out thrombosis in the deep venous system.

Preparation

The technician explains the procedure to the patient.
The patient takes place on the examination-bench, with bare legs, in supine position. Ensure that the patient is as relaxed as possible, with the upper body slightly elevated.

Method

The veins are imaged transversely from the ligament of Poupart to the ankle. By applying pressure with the probe the compressibility of the vein is evaluated. The vessel's patency is evaluated by the assessment of flow.
The vein is examined over the entire length at intervals of 5 centimeters.

<u>Investigation of these veins is performed:</u>
Common femoral vein
Deep femoral vein
Superficial femoral vein
Popliteal vein
Gastrocnemius vein
Anterior tibial vein
Posterior tibial vein
Soleal vein

When thrombosis of the common femoral vein is detected, the vein is examined up to intra-abdominally. The iliac system will also be reviewed and optionally the vena cava.

Documentation

All examined veins should be photographically captured using the dual mode: the left image without compression, the right image with compression.
The technician fills out the Case Report Form PROTECT and concludes whether thrombosis is present or not. When thrombosis is present the exact location is documented.
The completed case report form should be filed with the images of the examination.

Results

The patient is informed of the outcome of the examination and is sent back to the surgical department. Generally the patient can go home, unless there is an (asymptomatic) DVT. In this case the patient should be referred to the emergency department.