ANTICOAGULANT THERAPY FOR SYMPTOMATIC CALF DEEP VEIN THROMBOSIS: THE CACTUS RANDOMISED PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background

The efficacy and safety of anticoagulant treatment for patients with acute, symptomatic calf deep vein thrombosis (DVT) is not established. We aimed to assess whether therapeutic anticoagulation is superior to placebo in patients with symptomatic calf DVT.

Methods

In a randomised, placebo-controlled trial, we assigned 259 outpatients without active cancer or previous venous thromboembolic disease to receive either the low-molecular-weight heparin nadroparin, administered subcutaneously at the dose of 171 UI/kg once daily, or placebo for six weeks. Central randomisation was performed using a computer generated randomisation list, stratified by study center. Random allocation sequences were centrally determined by an independent research clinical center. Sequentially numbered boxes including 42 syringes were delivered to the pharmacy of the enrolling centers. All boxes were tamper-proof, equal in weight and similar in appearance. Using a web based interface, the investigator received by e-mail the number of the box that had to be delivered to the patient. The primary efficacy outcome measure was the composite of extension of calf DVT to proximal veins, contralateral proximal DVT or pulmonary embolism at six weeks. The primary safety outcome measure was major or clinically relevant non major bleeding at 6 weeks. Patients were prescribed compression stockings and followed for 90 days. Both intention-to-treat and per-protocol analyses were performed. The trial was registered at ClinicalTrials.gov (NCT00421538).

Findings

Between February 1, 2008 and November 30, 2014, 746 patients were screened at 19 centers in three countries, and 259 patients were enrolled. The primary efficacy outcome occurred in 4 of 122 patients (3.3%) of the nadroparin arm and in 7 of 130 patients

(5.4%) of the placebo arm ($p=0.54$; risk difference -2.1% (95%CI: -7.8 to +3.5%)). Major or clinically relevant non-major bleeding occurred in 5 of 122 patients (4.1%) in the nadroparin arm and in 0 of 130 patients (0.0%) in the placebo arm ($p=0.03$; risk difference +4.1 (95% CI: +0.4 to +9.2%)). In the nadroparin arm, 1 patient died from metastatic cancer and one patient was diagnosed with heparin induced thrombocytopenia, type II.

Interpretation

The use of therapeutic doses of nadroparin for six weeks in low-risk outpatients with symptomatic calf DVT was not superior to placebo in reducing the risk of proximal extension or thromboembolic events, but was associated with a significantly higher risk of bleeding. To our knowledge, this is the first randomised, placebo-controlled trial in the field of calf DVT. Its main limitation is that the target sample size was not reached, resulting in limited statistical power. The study questions the necessity to treat all calf DVT with therapeutic anticoagulation. As calf DVT represents half of all diagnosed DVT, avoiding systematic anticoagulation could have a significant impact for the individual patient and from a public health perspective.

Funding

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BACKGROUND

Isolated calf deep vein thrombosis (DVT) (i.e. infra-popliteal DVT without extension to proximal veins or pulmonary embolism (PE)), also known as distal DVT, is frequent and represents up to 50% of all lower limb DVT.¹⁻³ Unlike proximal DVT and PE, which have been extensively studied and for which management is well standardized and the subject of high-level evidence and recommendations, much less is known on the optimal management of isolated calf DVT.⁴

As a result, there is significant variation in diagnostic and therapeutic practices across centers.^{1,5-8} In some centers, both the proximal veins and the calf veins are imaged in all patients with suspected DVT, and patients diagnosed with a calf DVT are treated with anticoagulant therapy.⁹ Other centers rely on serial imaging of the proximal veins only, and thus do not diagnose or treat calf DVT.^{10,11} In the case of a negative proximal ultrasound, the test is often repeated one week later to rule out extension of a calf DVT to proximal veins. Comparisons between these two diagnostic strategies have shown that the proportion of patients diagnosed with DVT and thus treated with anticoagulants was higher when using the whole-leg imaging as compared with serial proximal imaging. Moreover, diagnosing and treating distal DVT was not associated with better safety, as assessed by the three-month venous thromboembolism (VTE) risk.^{12,13} These results question the need to systematically treat calf DVT with anticoagulants, particularly in patients free of any of the major strong identified predictors of calf extension/recurrence (inpatients, patients with history of previous VTE or with cancer), who represent the majority of calf DVT patients.^{4,14}

To address this knowledge gap, we conducted the CACTUS (Compression versus Anticoagulant treatment and compression in symptomatic Calf Thrombosis diagnosed by UltraSound) trial, a randomised placebo-controlled trial of a six-week course of

therapeutic dose low-molecular weight heparin (nadroparin 171 UI/kg daily subcutaneously) versus placebo in outpatients with a first symptomatic calf DVT.

METHODS

Patients

Outpatients with an acute symptomatic objectively confirmed calf DVT were eligible to undergo randomisation. Outpatients were randomized either in University medical centers or by vascular physicians in community medical clinics. The diagnosis of DVT was established by compression ultrasonography (CUS). The criterion for calf DVT was the presence of an incompressible venous segment in deep calf (posterior tibial, peroneal, anterior tibial) or muscular veins (gastrocnemius or soleus). Patients with a thrombus limited to superficial veins were not eligible. Exclusion criteria included: less than 18 years of age, pregnancy, previous documented VTE, calf DVT associated with a proximal DVT (popliteal or more proximal) or a clinically suspected PE, active malignancy, another indication for long-term anticoagulation, thrombocytopenia (platelet count below 100 G/L), impaired renal function (serum creatinine above 180 μ mol/L or a creatinine clearance below 30 ml/min), known hypersensitivity to heparin, active bleeding or a condition associated with a high risk of bleeding (gastric ulcer, cerebral malignant disease), or a body weight above 115 Kg or below 40 Kg. Patients were also excluded if they had already received therapeutic doses of anticoagulants for more than 2 days or had an ongoing requirement for thromboprophylaxis, were using daily non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin accepted if $\leq$ 160 mg/daily), if they were enrolled in another trial in the previous 30 days, or if they were unable or unwilling to provide informed consent.

The study was approved by the Ethics Committee of all participating centers and registered on ClinicalTrials.gov (NCT00421538).

Study design

We conducted an international (Canada, France, Switzerland), multicentre, placebo-controlled, randomised clinical trial. Central randomisation was performed using a computer generated randomisation list, stratified by study center. Random allocation sequences of variable block size were centrally determined by an independent research clinical center. Sequentially numbered boxes including 42 syringes were delivered to the pharmacy of the enrolling centers. All boxes were tamper-proof, equal in weight and similar in appearance. Using a web based interface, the investigator received by e-mail the number of the box that had to be delivered to the patient. The patients were randomly assigned in a 1:1 ratio to receive nadroparin 171 UI/Kg daily, or an identically packaged placebo injection (sterilized NaCl 0.9%), administered subcutaneously for 42 days. All study personnel and participants were masked to group assignment.

The duration of anticoagulant treatment was based on findings from two large randomised trials, which demonstrated that 6 weeks of anticoagulant treatment was not statistically inferior to 3 months in terms of VTE recurrence and safer in terms of bleeding risk in case of isolated calf DVT.^{15,16}

Nadroparin and placebo were packaged in identical boxes containing 42 identical pre-filled syringes containing either nadroparin calcium or placebo. The study drug was provided as in-kind support purchased from GlaxoSmithKline France and Aspen Pharma. The maximum interval between the qualifying ultrasonographic study and randomisation was 36 hours. Patients were taught how to do self-injections by the study

personnel and were prescribed and instructed to use graduated elastic compression stockings daily.

General characteristics, risk factors, signs and symptoms were collected using a standardized case report form. A detailed description of the ultrasound results was also captured, including affected venous segment, diameter of the thrombosed vein under compression, and length of the thrombus. Numerical images were stored electronically. In-person follow-up visits were scheduled at day 3-7 and at 6 weeks, prior to discontinuation of the study drug. The follow-up visits comprised a clinical assessment and a bilateral whole-leg CUS. Patients were instructed to contact the study personnel at any time in case of any new or worsening symptom. Patients found to have a recurrent symptomatic thromboembolic event were removed from the study and given standard anticoagulant treatment. Apart from the three CUS tests reported in the study, no radiographic assessments were performed. Laboratory monitoring consisted in a monthly platelet blood count to detect heparin induced thrombocytopenia.

Finally, a telephone follow-up visit was performed 3 months after inclusion in the study. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by independent ethics committees, and written informed consent was obtained from all patients before they underwent randomisation. The study was funded by the Swiss National Science Foundation in Switzerland, by the Programme Hospitalier de Recherche Clinique in France, by the Canadian Institutes of Health Research in Canada, and by a grant from the 2007 International Society on Thrombosis and Haemostasis (ISTH) Presidential Fund. A steering committee was responsible for the design, conduct, and reporting of the study. The members of the writing committee wrote the first draft of the manuscript and made the decision to submit the manuscript for publication. All the authors

contributed to the writing of subsequent drafts of the manuscript, had full access to the data and analyses, and vouch for the accuracy and completeness of the report, as well as the fidelity of the study to the protocol and statistical analysis plan. The study was registered on ClinicalTrials.gov (NCT00421538).

Study outcomes

The primary outcome was the composite of extension of calf DVT to proximal veins, contralateral proximal DVT, or a symptomatic PE at six weeks.

The secondary outcomes comprised the individual components of the composite primary outcome at 6 weeks and at 3 months: extension of calf DVT to proximal veins or contralateral proximal DVT at 6 weeks and three months, symptomatic PE at 6 weeks and 3 months; major bleeding or clinically non relevant major bleeding, death, and serious adverse events at 6 weeks and 3 months. These outcomes were selected as they represent the main potential complications of a distal DVT, i.e. the occurrence of a major VTE (proximal DVT, PE, death from PE), and the main complications of anticoagulant therapy. Moreover, these outcomes are similar to those used in similar trials in the field of VTE. Efficacy and safety outcomes were assessed at the end of treatment (6 weeks) as in most therapeutic studies. However, as the three-month thromboembolic rate has become a standard to assess the safety of diagnostic strategies in the field of VTE, efficacy and safety outcomes were also assessed three months after inclusion.

DVT extension was defined as ultrasonographically proven extension to the popliteal, femoral, iliac and cava veins. Contralateral proximal DVT was diagnosed either on planned CUS between day 3-7, at day 42, or in patients evaluated for clinically suspected DVT, using standard CUS. PE was diagnosed in patients with clinically

suspected PE using widely accepted criteria: pulmonary artery intraluminal filling defect on a computed tomography pulmonary angiography, high probability ventilation perfusion lung scan or positive pulmonary angiogram. Major bleeding was defined using the ISTH criteria.¹⁷

Clinically relevant non-major bleeding (CRNMB) was defined as a bleeding that does not fit the criteria for the ISTH definition of major bleeding but which meets at least one of these criteria: 1) requires medical intervention 2) leads to hospitalization 3) induces a face to face consultation. All suspected outcomes were reviewed by a central adjudication committee whose members were unaware of group assignment.

Statistical analysis

General characteristics of the study population were described using mean and standard deviation for numerical variables, and number and proportions for categorical variables. Efficacy and safety analyses were performed on data from the intention-to-treat population. The primary outcome rates in the two arms were compared using a chi-2 test, or a Fisher exact test, as appropriate. A per-protocol analysis for safety and efficacy was also conducted among patients who completed their allocated treatment. Analyses were performed using SPSS software (version 21.0, IBM corporation).

Sample size

We initially estimated that with a sample size of 286 patients in each group, the study would have 90% power to detect a 70% risk reduction in the rate of the primary efficacy outcome (conservative hypothesis), assuming an incidence of the primary outcome of 10% in the placebo group², at a two-sided 5% level of significance. However, the steering committee decided to discontinue the study in November 2014 after 259

patients were included, due to the expiration date of the remaining study drug, lack of funding to manufacture new batches of study drug, and slow recruitment rate.

Role of the funding source

The funding source of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The CONSORT flow-chart is depicted in Figure 1. Between February 1, 2008 and November 30, 2014, 746 patients were screened at 23 centers in three countries, and 259 patients were enrolled. Main reasons for non-inclusion were the inability or unwillingness to consent to the study (n=121), the presence of an associated proximal DVT or clinically suspected PE (n=90), an indication for long-term anticoagulation (e.g. atrial fibrillation) (n=61), impaired renal function (n=52), started on anticoagulant therapy for > 48 hours at the time of screening (n=49), previous DVT (n=48), active malignancy (n=43), active bleeding or condition associated with a high risk of bleeding (12), pregnancy (11).

After randomisation, 126 patients were allocated to the nadroparin group, and 133 to the placebo group. Baseline characteristics of included patients are depicted in Table 1. Overall, mean age was 53 years, and 127/259 (49%) were female. A total of 113 (44%) patients had a DVT involving the posterior tibial or peroneal vein whereas 143 (55%) had involvement of the gastrocnemius and/or soleus vein.

All patients received at least one dose of the study drug. There were three patients lost to follow-up, two in the nadroparin arm and one in the placebo arm. Moreover, four patients (two in each arm) withdrew their consent during the course of the study. Therefore, 122 patients were available for the intention-to-treat analysis in the nadroparin arm, and 130 in the placebo arm. Finally, 17 patients (11 in the nadroparin arm and 6 in the placebo arm) did not complete the six-week treatment period, leaving 111 and 124 patients for the per-protocol analysis in the nadroparin and in the placebo arm, respectively. The study flow-chart is depicted in Figure 2. In the nadroparin arm, 61 patients out of 126 had a tibial posterior or peroneal vein thrombosis and 63 had a muscle vein thrombosis (missing value n=2). In the placebo arm 52 patients out of 133 had a tibial posterior or peroneal vein thrombosis and 80 patients had a muscle vein thrombosis (missing value n=1).

Clinical outcomes

The primary efficacy outcome (composite of extension of calf DVT to proximal veins, contralateral proximal DVT, or symptomatic PE at six weeks) occurred in 4 of 122 patients (3.3%) in the nadroparin arm and in 7 of 130 patients (5.4%) in the placebo arm ($p=0.54$), risk difference -2.1% (95% confidence interval: -7.8 to +3.5%) (Table 2). DVT extension was detected on the scheduled serial ultrasound at Day 3-7 in one patient (0.8%) in the nadroparin arm, and 3 patients (2.3%) in the placebo arm. Five additional patients (1 in the nadroparin arm and 4 in the placebo arm) were diagnosed with proximal extension during the six-week follow-up period. Finally, two patients (1.6%) in the nadroparin arm developed a non-fatal symptomatic PE. There was no difference in the primary outcome rate in patients with an isolated muscular calf DVT (i.e.

gastrocnemius or soleus vein thrombosis) as compared with patients with peroneal or posterior tibial calf DVT.

In the per-protocol analysis, 11 patients in the nadroparin arm discontinued their intervention prematurely [initiation of anticoagulant therapy for a non-adjudicated VTE (n=2), initiation of thromboprophylaxis for another indication (n=1), discontinuation of study medication (n=2), skin rash (n=3), bleeding (n=2), heparin induced thrombocytopenia type II confirmed by a platelet serotonin release test (n=1)], and 6 patients in the placebo arm [initiation of anticoagulant therapy for a non-adjudicated VTE (n=3), stopped the medication (n=2), inadequate compliance (n=1)]. No patient had a dose reduction during the course of the study. Among patients who completed the intervention, the primary efficacy outcome was observed in 4 of 111 patients (3.6%) in the nadroparin arm, and in 7 of 124 patients (5.6%) in the placebo arm (p=0.46), risk difference -2.0% (95% CI: -8.0 to +4.0%). The net clinical benefit balancing VTE against major and clinically-relevant non-major bleeding events was as follows: 9/122 (7.4%, 95% CI: 3.9-13.4%) in the nadroparin arm and 7/130 (5.4%, 95%CI 2.6-10.7%) in the placebo arm (risk difference: +2.0 (95% CI - 4.3% to +8.6%)).

Moreover, 5 patients in the placebo arm, and no patient in the nadroparin arm, were diagnosed with an asymptomatic calf DVT on the study-mandated Day 42 ultrasound. Two of them were started on anticoagulant therapy. None of these 5 patients had an adjudicated VTE by Day 90.

Major or clinically relevant non-major bleeding occurred in 5 of 122 patients (4.1%) in the nadroparin arm (1 major and 4 clinically relevant non-major bleeding events) and in 0 of 130 patients (0.0%) in the placebo arm (p=0.03), risk difference +4.1 (95% CI: +0.4 to 9.2%) (Table 3). Moreover, one patient in the nadroparin arm (0.8%) had confirmed heparin-induced thrombocytopenia.

Between day 42 and day 90, there were no additional adjudicated VTE events in the nadroparin arm. In the placebo arm, one patient was diagnosed with a non-fatal symptomatic PE on Day 89.

Two patients, one in each group, developed a new symptomatic calf DVT between day 42 and day 90, after completing their allocated treatment and were started on anticoagulant therapy. There were no new bleeding episodes in any arm. One patient in the nadroparin arm died from a non-VTE related death (cancer) at Day 80. This patient was found to have a pancreatic metastatic cancer, diagnosed few days after inclusion in the study, with catastrophic progression and death within few weeks. No other adverse events were reported in the study.

DISCUSSION

Six weeks of therapeutic doses of nadroparin are not superior to placebo to prevent extension of calf DVT to proximal veins, contralateral proximal DVT and symptomatic PE and significantly increase the rate of major and clinically relevant non major bleeding in patients with a first symptomatic calf DVT.

Whether calf DVT requires anticoagulant therapy is currently one of the most debated issues in the field of venous thromboembolic disease. Although calf DVT is a very common medical condition, no randomised placebo-controlled trials have addressed its treatment to date. The results of this first multicenter, placebo-controlled, randomised trial suggest that the systematic use of therapeutic anticoagulant therapy might not be warranted for all patients with symptomatic calf DVT. Indeed, the net clinical benefit balancing VTE against major and clinically-relevant non-major bleeding events demonstrated that 9/122 (7.4%, 95% CI: 3.9-13.4%) and 7/130 (5.4%, 95%CI 2.6-10.7%) events occurred in the nadroparin and placebo arms, respectively (risk

difference: +2.0 (95% CI - 4.3% to +8.6%)). Our results challenge those reported by Lagerstedt 30 years ago when, as compared with no warfarin, 3 months of warfarin treatment significantly decreased the rate of proximal extension from 29% to 0%.¹⁸ However, Lagerstedt's study population significantly differs from ours: most of DVT extensions (5/8) reported in Lagerstedt study occurred in high-risk patients with previous history of VTE, a population excluded from our study.

Our results are in line with those observed in a small open label trial. In a population of 107 patients with muscular DVT at low risk of proximal extension (almost exclusively outpatients without cancer), Schwarz et al. showed that the risk of proximal extension at 3 months was similar (3.7%) after a course of 10 days of therapeutic nadroparin and elastic compression stockings compared to patients who only wore elastic compression stockings.¹⁹

Our results are also consistent with the vast amount of previously published diagnostic studies showing that it is safe to not initiate anticoagulant therapy in patients who had DVT ruled out after a negative serial proximal ultrasound of the lower extremity.^{10,12,20,21} Moreover, in clinical trials comparing whole-leg imaging versus serial proximal imaging, the use of whole-leg ultrasound was associated with a significantly higher number of diagnosed -and thus, treated- DVT involving the calf veins, without a decrease in the three-month thromboembolic rate in patients considered as not having DVT after the initial ultrasound assessment.^{1,12,13} In our study, three out of seven proximal extensions in the placebo arm were detected by the systematic serial ultrasound at Day 3-7. Therefore, the risk of adjudicated VTE after a negative serial proximal CUS in the placebo arm was 4/130 (3.1%, 95%CI: 1.2-7.6%), as compared to 3/122 (2.5%, 95% CI: 0.8-7.0%) in the nadroparin arm (risk difference: -0.6 (-5.5 to +4.3%)). Thus, our data support the American College of Chest Physicians guidelines, which suggest that low-

risk patients with symptomatic calf DVT, such as patients without a previous DVT or active malignancy, could safely be managed with serial ultrasound testing and no anticoagulant therapy.⁴ Interestingly there was no obvious differences in the rates of proximal extensions between muscular and calf DVT and the anatomical distribution of calf DVT was similar to that reported in large observational studies, suggesting an absence of selection bias on this important criterion.

Our study has limitations that are important to acknowledge. First, we were not able to reach our target sample size of 572 patients. Indeed, the steering committee decided to discontinue the study in November 2014 after 259 patients were included, due to expiration date of the study drug, lack of funding to manufacture new batches of study drug, and slow recruitment rate. As a consequence, our study is underpowered and the 95% confidence intervals around the proportion estimates were wider than expected. It should be pointed out that the number of events in the placebo arm was much lower than expected (5.4% vs. 10.0%). Therefore, it would have been necessary to include 1891 patients in each arm to have the initial scheduled power (90%); if we had included the expected number of patients (n=572) our power would have been of only 23%. Thus a larger recruitment would probably not have changed the trend of our results. The low inclusion rate reported in this study is multifactorial and deserves some comments. As the benefit of treating calf DVT with anticoagulants is highly debated, we initially drafted the protocol to include only low-risk patients, i.e. outpatients without cancer or previous VTE. This is likely the main reason for the slow recruitment rate. The study comprised a placebo arm, which was often a reason for patients to deny participation in the study. Both placebo and nadroparin were administered as a six-week course of subcutaneous injections, which was considered cumbersome by many patients, even more after direct oral anticoagulants became available. Also, the study was quite demanding for patients,

as in addition to the three-month follow-up, it also included visits in the clinic for a CUS at day 3 to 7 and at six weeks.

Second, we excluded patients with previous documented VTE, inpatients, and patients with cancer. Therefore, our results are not generalizable to these high risk patients. Finally, all patients underwent a bilateral CUS at day 42. The aim of this ultrasound was to detect extension of calf DVT to the proximal veins, which was one of the components of the study's primary outcome. Although only patients with proximal DVT were adjudicated as meeting the study endpoints, some patients were started on anticoagulants on the basis of the finding of an asymptomatic calf DVT on systematic CUS at Day 42. This might have led to an underestimation of the actual three-month VTE risk. It is noteworthy that all five patients diagnosed with an asymptomatic calf DVT at Day 42 were in the placebo arm. Two were started on anticoagulant therapy, and all five had an uneventful follow-up.

What are the clinical implications of our findings? First, our data suggest that the systematic use of anticoagulant therapy for all patients with calf DVT might not be warranted. The absence of serious thromboembolic events in the placebo group (no symptomatic PE at 6 weeks in 130 patients), combined with the significantly increased risk of bleeding in the nadroparin group is, in our view, a strong argument in favor of not systematically treating calf DVT with anticoagulants. The net clinical benefit shows no clear advantage of anticoagulant therapy over placebo in our cohort of low-risk outpatients. Monitoring with ultrasound surveillance appears to be a reasonable alternative to anticoagulant therapy. Not treating with anticoagulants all calf DVT could be an important cost-saving strategy, as calf DVT represents half of diagnosed DVT according to a recent meta-analysis.⁹ Whether a prophylactic dose of anticoagulants could be an alternative remains to be determined. In patients with superficial vein

thrombosis, a prophylactic dose was associated with a reduction in the rate of thromboembolic complications, without any increase in the risk of bleeding.²² Recent approval of the direct oral anticoagulants (DOACs) could also impact future strategies. Until recently, the use of anticoagulants in patients with calf DVT was limited by either the cost and invasiveness of daily low molecular weight heparin injections, or the cumbersome initiation and management of warfarin therapy. However, the risk-benefit balance of DOACs has not been evaluated for this indication as of yet, and large prospective trials are needed. Second, the risk of symptomatic VTE was very low in both study arms between completion of study drug at 42 days and follow-up at 90 days. Therefore, if a patient is started on treatment for a symptomatic calf DVT, a limited duration (i.e. six weeks) of anticoagulant therapy is likely to be sufficient. Third, our results are in line with the results of diagnostic studies, demonstrating the safety of not imaging calf veins in patients with suspected DVT in whom proximal DVT has already been excluded.

In conclusion, the use of therapeutic doses of nadroparin for six weeks in patients with symptomatic calf DVT was not superior to placebo in reducing the risk of proximal extension or other VTE complications, but was associated with a significantly higher risk of bleeding. Our results might not apply to high-risk patients, such as patients with previous VTE, active malignancy or inpatients. Ultrasound surveillance appears to be a reasonable alternative to the use of anticoagulants in low-risk patients with a first symptomatic calf DVT. Use of prophylactic dose of anticoagulants could constitute another alternative but needs to be assessed in a clinical trial.

AUTHOR'S CONTRIBUTIONS

M. Righini, G. Le Gal, J.P. Laroche, I. Quéré J.P. Galanaud, S.R. Kahn: designed research, performed research, collected data, analyzed data and wrote the paper. H. Guenneguez, D. Brisot, A. Diard, P. Faisse, M.T. Barrelier, C. Hamel-Desnos, C. Juras, O. Pichot, M. Martin, L. Mazzolai, C. Choquenot, S. Accassat, M. Carrier, G. Le Gal, B. Mermillod, J.P. Laroche, H. Bounameaux, A. Perrier, S.R. Kahn, I. Quéré, H. Robert-Ebadi: performed research, collected data, analyzed data and wrote the paper. M. Righini, G. Le Gal, J.P. Laroche, I. Quéré, J.P. Galanaud, S.R. Kahn, A. Perrier, H. Bounameaux: designed research, performed research, collected data, analyzed data and wrote the paper.

L. Mazzolai, G. Le Gal, H. Bounameaux, A. Perrier, S.R. Kahn, I. Quéré and M. Righini are full professors

DECLARATION OF INTERESTS

We declare no competing interests

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The trial was registered at ClinicalTrials.gov (NCT00421538).

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Table 1. Baseline characteristics of the study patients.

	Nadroparin arm N=126	Placebo arm N=133
Demographic data		
Female Gender, n (%)	64 (51%)	63 (47%)
Male Gender, n (%)	62 (49%)	70 (53%)
Age, years (mean±SD)	52 (±17)	53 (±17)
Risk factors of DVT		
Familial history of VTE, n (%)	24 (19%)	24 (18%)
Active malignancy, n (%)	3 (2%)	2 (2%)
Estrogen use, n (%)	21 (17%)	22 (17%)
Surgery, n (%)	12 (10%)	14 (14%)
Plaster immobilization, n (%)	9 (7%)	6 (5%)
Travel >6 hours, n (%)	14 (11%)	20 (15%)
Post-partum, n (%)	2 (2%)	0 (0%)
Bedrest, n (%)	14 (10%)	10 (8%)
Concomitant medications		
Compliance with ECS > 70%		
- Day 7, n,%	103/117 (89%)	106/126 (84%)
- Day 42, n,%	82/110 (75%)	95/122 (78%)
Daily use of aspirin		
- Day 1	10/120 (5%)	10/122 (10%)
- Day 42	5/112 (5%)	8/123 (7%)

Oral nonsteroidal anti-inflammatory drugs or COX-2 inhibitors use		
- Day 1	10/120 (5%)	3/131 (2%)
- Day 42	4/112 (4%)	1/123 (1%)

ECS: Elastic compression stockings

Table 2. Efficacy outcomes by day 42 and day 90 (intention to treat analysis).

	Therapeutic Nadroparin (N=122)	Placebo (N=130)	Absolute Risk difference, %, (95% CI)	P Value
Primary outcome by Day 42	4 (3.3%)	7 (5.4%)	-2.1 (-7.8 to +3.5)	0.54
Proximal DVT	2 (1.6%)	7 (5.4%)	-	-
Pulmonary embolism	2 (1.6%)	0 (0.0%)	-	-
Secondary outcome by Day 90	4 (3.3%)	8 (6.2%)	-2.9 (-8.7 to +2.8)	0.28
Proximal DVT	2 (1.6%)	7 (5.4%)	-	-
Pulmonary embolism	2 (1.6%)	1 (0.8%)	-	-

Primary efficacy outcome measure: extension of calf DVT to proximal veins, contralateral proximal DVT or pulmonary embolism.

Table 3. Safety outcomes by day 42.

	Therapeutic Nadroparin (N=122)	Placebo (N=130)	Absolute Risk difference, %, (95% CI)	P Value
Major bleeding or non-major clinically relevant bleeding	5 (4.1%)	0 (0.0%)	+4.1 (+0.4 to +9.2)	0.03
Major bleeding	1 (0.8%)	0 (0.0%)	-	-
Non-major clinically relevant bleeding	4 (3.3%)	0 (0.0%)	-	-
Death	0 (0.0%)	0 (0.0%)	-	-
Other adverse events			-	-
-Skin reactions	3 (2.5%)	0 (0.0%)	-	-
-Heparin induced thrombocytopenia	1 (0.8%)	0 (0.0%)	-	-

Figure 1. CONSORT flow-chart

Figure 2: study flow-chart

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