Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial

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Summary

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

Methods In this randomised, double-blind, placebo-controlled trial, we enrolled low-risk outpatients (without active cancer or previous venous thromboembolic disease) with a first acute symptomatic DVT in the calf from 23 university medical centres or community medical clinics in Canada, France, and Switzerland. We randomly assigned (1:1) patients to receive either the low-molecular-weight heparin nadroparin (171 UI/kg, subcutaneously, once a day) or placebo (saline 0·9%, subcutaneously, once a day) for 6 weeks (42 days). Central randomisation was done using a computer-generated randomisation list, stratified by study centre. Random allocation sequences of variable block size were centrally determined by an independent research clinical centre. Study staff, patients, and outcome assessors (central adjudication committee) were masked to group assignment. Numbered boxes of active drug or placebo were provided to pharmacies in identical packaging. All patients were prescribed compression stockings and followed up for 90 days. The primary efficacy outcome was a composite measure of extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism at day 42 in the modified intention-to-treat population. The primary safety outcome was major or clinically relevant non-major bleeding at day 42. The trial was registered with ClinicalTrials.gov, number NCT00421538.

Findings Between Feb 1, 2008, and Nov 30, 2014, we screened 746 patients, enrolling 259 patients (50% of the prespecified sample size), before the trial steering committee terminated the trial because of expiry of study drug and slow recruitment. The intention-to-treat analysis population comprised 122 patients in the nadroparin group and 130 in the placebo group. There was no significant difference between the groups in the composite primary outcome, which occurred in four patients (3%) in the nadroparin group and in seven (5%) in the placebo group (risk difference −2·1%, 95% CI −7·8 to 3·5; p=0·54). Bleeding occurred in five patients (4%) in the nadroparin group and no patients in the placebo group (risk difference 4·1%, 95% CI 0·4 to 9·2; p=0·0255). In the nadroparin group one patient died from metastatic pancreatic cancer and one patient was diagnosed with heparin-induced thrombocytopenia type 2.

Interpretation Nadroparin was not superior to placebo in reducing the risk of proximal extension or venous thromboembolic events in low-risk outpatients with symptomatic calf DVT, but did increase the risk of bleeding. Avoidance of systematic anticoagulation for calf DVT could have a substantial impact on individual patients and from a public health perspective.

Funding Swiss National Science Foundation, the Programme Hospitalier de Recherche Clinique in France, and the Canadian Institutes of Health Research.

Introduction Isolated calf deep vein thrombosis (DVT; ie, infra-popliteal DVT, without extension to proximal veins or pulmonary embolism, also known as distal DVT) represents up to 50% of all lower-limb DTVs and is thought to have low embolic potential.1–3 Unlike proximal DVT and pulmonary embolism, which have been extensively studied and have high-level evidence and recommendations for management, much less is known about the optimum management of isolated calf DVT.4 As a result, diagnostic and therapeutic practices substantially vary across centres.1–4 In some centres, both the proximal veins and the calf veins are imaged (so-called whole-leg imaging) in all patients with suspected DVT; and patients diagnosed with a calf DVT are treated with anticoagulant therapy.5 Other centres rely on serial imaging of the proximal veins only, and thus do not diagnose or treat calf DVT.6,7 In the case of a negative proximal ultrasound, the test is often repeated 1 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
Research in context

Evidence before this study

Knowledge about the optimum management of isolated calf deep vein thrombosis (DVT) remains scarce, resulting in major variation in diagnostic and therapeutic methods across centres and countries. Investigators have questioned the need to systematically treat calf DVT with anticoagulants, particularly in patients free of any of the major strong identified predictors of calf extension or venous thromboembolism recurrence (inpatients, patients with history of previous venous thromboembolism, or those with cancer), who represent most people presenting with calf DVT. The CACTUS trial is a randomised placebo-controlled trial of a 6 week course of therapeutic dose low-molecular-weight heparin versus placebo in outpatients with a first symptomatic isolated DVT. When planning this trial, we searched for all diagnostic and therapeutic studies, as well as systematic reviews, about calf DVT. We searched PubMed and Embase for papers published in English, French, German, and Italian between Jan 1, 1985, and Jan 31, 2008 (the start of the CACTUS study), using the search terms: “calf DVT”, “distal DVT”, “pulmonary embolism”, “anticoagulation”, “anticoagulant treatment”, “placebo”, and “randomized study”.

Our search found few studies. We found only one randomised study (published in 1985) that specifically studied the value of anticoagulant treatment of calf DVT. However, it was an open-label study that included a small number of patients (n=58) who were at particularly high-risk of recurrence. Moreover, it used diagnostic instruments that are now outdated. Therefore, although isolated calf DVT is a frequent diagnosis in patients with suspected DVT and leads to wide prescription of anticoagulant treatment by many vascular medicine specialists, there is little robust evidence supporting a positive benefit–risk ratio for anticoagulants.

Added value of this study

To our knowledge, the CACTUS trial is the first randomised placebo-controlled trial for calf DVT. We show that therapeutic anticoagulation with low-molecular-weight heparin is not superior to placebo in reducing the risk of proximal extension or thromboembolic events in low-risk outpatients with symptomatic calf DVT, and is associated with a significantly higher risk of bleeding.

Implications of all the available evidence

Our findings question the necessity to treat all calf DVT with therapeutic anticoagulation. Because calf DVT is a frequently encountered entity in vascular medicine (half of all diagnosed DVTs), avoiding systematic anticoagulation could have a large effect on the individual patient and from a public health perspective. Indeed, patients with calf DVT and a low-risk profile for extension or recurrence could be treated with compression stockings without therapeutic-dose anticoagulation. The necessity and benefit–risk ratio of anticoagulant treatment for calf DVT in high-risk patients (inpatients, patients with cancer, and patients with previous venous thromboembolism) should be evaluated in future studies.

Methods

Study design and participants

We did this randomised, double-blind, placebo-controlled trial in 23 centres in Canada, France, and Switzerland (appendix). We enrolled outpatients with a first, acute, symptomatic, objectively confirmed calf DVT who presented to university medical centres or community medical clinics. The diagnosis of DVT was established by whole-leg compression ultrasonography. The criterion for calf DVT was the presence of an incompressible venous segment in deep calf veins (posterior tibial, peroneal, or anterior tibial) or muscular veins (gastrocnemius or soleus). Patients with a thrombus limited to superficial veins were not eligible. We also did not include people younger than 18 years of age, pregnant women, and patients with the following: previous documented venous thromboembolism, calf DVT associated with a proximal DVT (popliteal or more proximal) or a clinically suspected pulmonary embolism, active or recent (<6 months) malignancy, another indication for long-term anticoagulation, thrombocytopenia (platelet count lower than 100×10⁹ platelets per L), impaired renal function (serum creatinine higher than 180 μmol/L or a creatinine clearance lower than 30 mL per min), known hypersensitivity to heparin, active bleeding or a condition associated with a high risk of bleeding (gastric ulcer, cerebral malignant disease), or a bodyweight higher than 115 kg or lower than 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 therapeutic anticoagulation. Because calf DVT is a frequently encountered entity in vascular medicine (half of all diagnosed DVTs), avoiding systematic anticoagulation could have a large effect on the individual patient and from a public health perspective. Indeed, patients with calf DVT and a low-risk profile for extension or recurrence could be treated with compression stockings without therapeutic-dose anticoagulation. Our findings question the necessity to treat all calf DVT with therapeutic anticoagulation. Because calf DVT is a frequently encountered entity in vascular medicine (half of all diagnosed DVTs), avoiding systematic anticoagulation could have a large effect on the individual patient and from a public health perspective. Indeed, patients with calf DVT and a low-risk profile for extension or recurrence could be treated with compression stockings without therapeutic-dose anticoagulation. The necessity and benefit–risk ratio of anticoagulant treatment for calf DVT in high-risk patients (inpatients, patients with cancer, and patients with previous venous thromboembolism) should be evaluated in future studies.
Hg) daily. Investigators collected to use graduated elastic compression stockings (30 mm by the study personnel and were prescribed and instructed compression, and length of the thrombus. N venous segment, diameter of the thrombosed vein under results was also captured in the form, including aff ected case report form. A detailed description of the ultrasound risk factors, signs, and symptoms using a standardised assessment and a bilateral whole-leg compression images were stored electronically. In-person follow-up visits were scheduled at days 3–7 and at day 42. Follow-up visits comprised a clinical assessment and a bilateral whole-leg compression ultrasonography. 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. No other imaging assessments were done. In-hospital laboratory monitoring consisted of a monthly platelet blood cell count to detect heparin-induced thrombocytopения. Finally, a telephone follow-up visit was performed 90 days after inclusion in the study.

**Outcomes**

The primary efficacy outcome was a composite endpoint of extension of calf DVT to proximal veins, contralateral proximal DVT, or symptomatic pulmonary embolism at day 42 after randomisation. Prespecified secondary outcomes were the individual components of the composite endpoint at day 42 and day 90 (extension of calf DVT to proximal veins, contralateral proximal DVT, or symptomatic pulmonary embolism). The primary safety outcome was the number of patients with major bleeding or clinically relevant non-major bleeding at day 42 and at day 90. Other safety outcomes were death and serious adverse events at day 42 and day 90. The protocol also specified assessment of post-thrombotic syndrome and quality of life scores at 1 year, which will be reported separately.

We selected these outcomes because they represent the main potential complications of a distal DVT—ie, the occurrence of a major venous thromboembolism (proximal DVT, pulmonary embolism, and death from pulmonary embolism), and the main complications of anticoagulant therapy. Moreover, these outcomes are similar to those used in similar trials of venous thromboembolism. Efficacy and safety outcomes were assessed at the end of treatment (6 weeks) as in most therapeutic studies. However, because the 3 month thromboembolic rate has become a standard to assess the safety of diagnostic strategies, efficacy and safety outcomes were also assessed 3 months after inclusion.

DVT extension was defined as ultrasonographically proven extension to the popliteal, femoral, iliac, and cava veins. Pulmonary embolism was diagnosed in patients under clinically suspicion with use of the following criteria: pulmonary artery intraluminal filling defect on a CT pulmonary angiography, high-probability ventilation perfusion lung scan, or positive pulmonary angiogram. Major bleeding was defined using the International Society on Thrombosis and Haemostasis (ISTH) criteria. Clinically relevant non-major bleeding was defined as a bleeding that does not fit the criteria for the ISTH definition of major bleeding but which met at least one of these criteria: requires medical intervention, leads to hospitalisation, or 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**

We 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 group, at a two-sided 5% level of significance. However, the trial steering committee decided to discontinue the study on Nov 1, 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. Efficacy and safety analyses were done in the modified intention-to-treat population (all patients who received one dose of study drug, excluding those who withdrew...
consent or were lost to follow-up). Primary outcome data were compared using a Fisher exact test. Secondary and safety outcome data were assessed with χ² or a Fisher exact test as appropriate. The net clinical benefit was computed as the addition of efficacy and safety events in both arms of the study. A per-protocol analysis for safety and efficacy was also planned for patients who completed their allocated regimen. We analysed data with SPSS software, version 21.0.

A steering committee was responsible for the design, conduct, and reporting of the study. The trial was registered with ClinicalTrials.gov, number NCT00421538.

Figure: Trial profile


Role of the funding source

The funding sources 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

Between Feb 1, 2008, and Nov 30, 2014, 746 patients were screened, with 259 enrolled (figure). 126 patients were randomly assigned to nadroparin and 133 to placebo (table 1), with the modified intention-to-treat analysis comprising 122 patients in the nadroparin group and 130 in the placebo group.

The primary efficacy outcome (composite of extension of calf DVT to proximal veins, contralateral proximal DVT, or symptomatic pulmonary embolism at 6 weeks) occurred in four patients (3%) in the nadroparin group and seven (5%) in the placebo group, with a non-significant risk difference (–2.1%; 95% CI –7.8 to 3.5; p=0.54; table 2). DVT extension was detected on the serial ultrasound at day 3–7 in one patient (<1%) in the nadroparin group and three (2%) in the placebo group. Five additional patients (one <1% in the nadroparin group and four [3%] in the placebo group) were diagnosed with proximal extension during the 6 week (42 day) follow-up period. Two patients (2%) in the nadroparin group developed a non-fatal symptomatic pulmonary embolism.

The proportion of patients with the primary outcome did not seem to differ between patients with an isolated muscular calf DVT (ie, gastrocnemius or soleus vein thrombosis) and those with a peroneal or posterior tibial calf DVT. In the per-protocol analysis, the primary efficacy outcome occurred in four (4%) of 111 patients who received nadroparin and in seven (6%) of 124 who received placebo (p=0.46), with a risk difference of –2.0% (95% CI –8.0 to 4.0).

Five (4%) patients in the placebo group were diagnosed with an asymptomatic calf DVT on the study-mandated day 42 ultrasound. Two were started on anticoagulant therapy. None of these patients had an adjudicated venous thromboembolism by day 90. Risk of adjudicated venous thromboembolism after a negative second compression ultrasonography at proximal level was 3.1% (95% CI 1.2–7.6; four of 130 patients) in the placebo group, as compared with 2.5% (95% CI 0.8–7.0; three of 122) in the nadroparin group (risk difference –0.6, –5.5 to 4.3).

Major or clinically relevant non-major bleeding occurred in five (4%) of 122 patients in the nadroparin group (one major and four clinically relevant non-major bleeding events) and no patients in the placebo group; risk difference 4.1% (95% CI 0.4 to 9.2; p=0.0255; table 3). One patient in the nadroparin group (<1%) had confirmed heparin-induced thrombocytopenia.
in the study, and had rapid progression and death within days. This patient was found to have metastatic non-venous-thromboembolism-related death (cancer) at days after inclusion.

One patient in the nadroparin group died from a thromboembolic event, a reported at a later date. No other therapy-related adverse events were reported in the study. Incidence of post-thrombotic syndrome and quality of life scores at 1 year will be reported at a later date.

### Discussion

Whether patients with calf DVT require anticoagulant therapy is one of the most debated issues in the field of venous thromboembolic disease. In this randomised, double-blind, placebo-controlled trial, nadroparin was not superior to placebo to prevent extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism, and led to significantly increased major and clinically relevant non-major bleeding events. Our findings suggest that the systematic use of therapeutic anticoagulation might not be warranted for all patients with symptomatic calf DVT. Indeed, the net clinical benefit balancing venous thromboembolism against major and clinically relevant non-major bleeding events did not significantly differ between the two study arms. Our results challenge those reported by Lagerstedt and colleagues in 1985 who reported that 3 months of open-label warfarin significantly decreased proximal extension from 29% with no treatment to 0% with warfarin. However, direct comparison between the two studies is limited by major differences in the study populations: most DVT extensions (five [63%] of eight patients) reported in Lagerstedt and colleagues’ study occurred in high-risk patients with previous history of venous thromboembolism, a population excluded from our study.

Our results are consistent with those reported in a small open-label trial of 107 patients with muscular calf DVT at low risk of proximal extension (almost exclusively outpatients without cancer). The investigators showed that the risk of proximal extension at 3 months was similar (3-7%) between patients given 10 days of therapeutic nadroparin and elastic compression stockings and those who only wore elastic compression stockings.

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**Table 1: Baseline characteristics and concomitant therapies**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Nadroparin group (n=126)</th>
<th>Placebo group (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of DVT</td>
<td>52 (40–65)</td>
<td>52 (41–68)</td>
</tr>
<tr>
<td>Posterior tibial or peroneal vein</td>
<td>61 (48%)</td>
<td>52 (39%)</td>
</tr>
<tr>
<td>Gastrocnemius or soleus vein or both</td>
<td>63 (50%)</td>
<td>80 (60%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**Table 2: Efficacy outcomes in the intention-to-treat population**

<table>
<thead>
<tr>
<th>Day 42</th>
<th>Nadroparin group (n=122)</th>
<th>Placebo group (n=130)</th>
<th>Absolute risk difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome* (primary outcome)</td>
<td>4 (3.3%)</td>
<td>7 (5.4%)</td>
<td>-2.1% (~7.8 to 3.5)</td>
<td>0.54</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2 (1.6%)</td>
<td>7 (5.4%)</td>
<td>-5%</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (1.6%)</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 90</th>
<th>Nadroparin group (n=130)</th>
<th>Placebo group (n=133)</th>
<th>Absolute risk difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome*</td>
<td>4 (3.3%)</td>
<td>8 (6.2%)</td>
<td>-2.9% (~8.7 to 2.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2 (1.6%)</td>
<td>7 (5.4%)</td>
<td>-5%</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Concomitant medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nadroparin group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECS (compliance &gt;70%)</td>
<td>10/112 (88%)</td>
<td>106/126 (84%)</td>
</tr>
<tr>
<td>Daily use of aspirin</td>
<td>10/120 (8%)</td>
<td>10/122 (9%)</td>
</tr>
<tr>
<td>Oral NSAIDs or COX-2 inhibitors</td>
<td>5/112 (4%)</td>
<td>8/123 (7%)</td>
</tr>
</tbody>
</table>

Data are n (%), median (IQR), or n/N (%), unless otherwise stated. DVT=deep vein thrombosis. VTE=venous thromboembolism. ECS=elastic compression stockings. NSAIDs=non-steroidal anti-inflammatory drugs.

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The net clinical benefit balancing venous thromboembolism against major and clinically relevant non-major bleeding events was as follows: nine of 122 patients (7.4%, 95% CI 3.9–13.4) in the nadroparin group and seven of 130 (5.4%, 2.6–10.7) in the placebo arm (risk difference 2.0%, -4.3 to 8.6).

Between day 42 and day 90 (the end of follow-up), there were no additional adjudicated venous thromboembolism events in the nadroparin group. In the placebo group, one patient was diagnosed with a non-fatality pulmonary embolism on day 89. Two patients, one in each group, developed a new non-major bleeding episode in any group.

One patient in the nadroparin group died from a symptomatic calf DVT after completing their allocated therapy and were started on anticoagulant therapy. There were no new bleeding episodes in any group. Two patients, one in each group, developed a new symptomatic calf DVT. In the nadroparin group, one patient was found to have metastatic pancreatic cancer, diagnosed a few days after inclusion in the study, and had rapid progression and death within a few weeks. No other therapy-related adverse events were reported in the study. Incidence of post-thrombotic syndrome and quality of life scores at 1 year will be reported at a later date.
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 leg.\textsuperscript{10,12,20,21} Moreover, in clinical trials comparing whole-leg imaging and serial proximal imaging, the use of whole-leg ultrasound was associated with a significant increase in diagnosed, and thus treated DVTs involving the calf veins, without a decrease in the 3 month thromboembolic rate in patients considered as not having DVT.\textsuperscript{10,12,21} In our study, three out of seven proximal extensions in the placebo group were detected by the systematic serial ultrasound at day 3–7; therefore, the risk of adjudicated venous thromboembolism after a negative serial proximal compression ultrasonography was 3% in both groups with a non-significant risk difference. Thus, our data support the American College of Chest Physicians guidelines,\textsuperscript{4} which suggest that low-risk patients with symptomatic calf DVT, such as those without a previous DVT or active malignancy, could be safely managed with serial ultrasound testing and no anticoagulant therapy.\textsuperscript{4} There were no obvious differences in the number of proximal extensions between patients with calf DVT involving the muscular veins (gastrocnemius, soleus) and those with calf DVT involving the posterior tibial or the peroneal veins. Moreover 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 and the steering committee decided to discontinue the study in November, 2014, after 259 patients were enrolled. As a consequence, our study is underpowered and the 95% CIs around the proportion estimates were wider than expected. Additionally, the number of events in the placebo arm was much lower than expected (5·4% vs the expected 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), the power would have only been 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. Because the benefit of treating calf DVT with anticoagulants is highly debated, we initially drafted the protocol to include only low-risk patients (ie, outpatients without cancer or previous venous thromboembolism), which is probably 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 6 week course of subcutaneous injections, which was considered cumbersome by many patients; even more so after direct oral anticoagulants became available. Also, the study was quite demanding for patients because in addition to the 3 months of follow-up, attendance at the clinic for a compression ultrasonography was mandated for two additional compression ultrasonography tests: at day 3–7 and at day 42.

Another limitation is that we excluded patients with previous documented venous thromboembolism, inpatients, and patients with cancer, making our results not generalisable to these high-risk patients. Finally, all patients underwent a bilateral compression ultrasonography 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 compression ultrasonography at day 42. This might have led to an underestimation of the actual 90 day venous thromboembolism 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.

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 pulmonary embolism 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 favour 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, in whom ultrasound surveillance seems to be a reasonable alternative to anticoagulant therapy. Avoidance of treating all calf DVTs with anticoagulants could be an important cost-saving strategy.\textsuperscript{9} Whether a prophylactic dose of anticoagulants could be an alternative remains to be established. 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.\textsuperscript{22} Approval of direct oral anticoagulants could also have an impact on future strategies.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
 & Nadroparin group (n=122) & Placebo group (n=130) & Absolute risk difference (95% CI) & p value \\
\hline
Major bleeding or non-major clinically relevant bleeding & 5 (4%) & 0 & 4·1 (0·4 to 9·2) & 0·0255 \\
Major bleeding & 1 (1%) & 0 & - & - \\
Non-major clinically relevant bleeding & 4 (3%) & 0 & - & - \\
Death & 0 & 0 & - & - \\
Other adverse events & & & & \\
Skin reactions & 3 (2%) & 0 & - & - \\
Heparin-induced thrombocytopenia & 1 (1%) & 0 & - & - \\
\hline
\end{tabular}
\caption{Safety outcomes at day 42}
\end{table}
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. The risk-benefit balance of direct oral anticoagulants has not yet been evaluated for this indication, and large prospective trials are needed.

Another interesting finding from our study is that the rate of symptomatic venous thromboembolic events is 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 (ie, 6 weeks) of anticoagulant therapy is likely to be sufficient. Finally, 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 in 6 weeks in patients with symptomatic calf DVT was not superior to placebo in reducing the risk of proximal extension or other venous thromboembolic 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 venous thromboembolism, 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.

Contributors
MR, J-PG, GLG, J-PL, SRK, and IQ designed the study. All authors conducted research, collected data, analysed data, and wrote the paper.

Declaration of interests
We declare no competing interests.

Acknowledgments
This study was supported by a grant from the Swiss National Science Foundation (number 32003B–104172), a grant from the Programme Hospitalier de Recherche Clinique (French Ministry of Health [PHRC] 20031409), a grant from the Canadian Institutes of Health Research (MOH-119524), and a grant from the 2007 International Society on Thrombosis and Haemostasis (ISTH) Presidential Fund. GLG holds a Faculty of Medicine Department of Medicine Chair on Diagnosis of Venous Thromboembolism and a Clinician Scientist Award from the Heart and Stroke Foundation of Ontario. Nadroparin and placebo were provided by GlaxoSmithKline France and Aspen. Stockings were provided to Canadian patients by Sigvaris. We express our gratitude to the members of the adjudication committee (Helia Robert-Elahi [Geneva University Hospital, Geneva, Switzerland], Sylvie Desmazais [Centre Hôpital Pierre-Boucher Longueuil, QC, Canada], and François Becker [retired], for their important contribution. We thank all physicians from the emergency departments and vascular medicine units of participating centres. We also thank all study nurses, secretaries, and clinical research associates for their invaluable help. We would also like to thank the Swiss Society of Angiology and the French Society for Vascular Medicine. Finally, we would like to express our gratitude to the patients who made the study possible.

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