

**Critical Review Form
Therapy**

PGY-1

[Schwarz T, Buschmann L, Beyer J, Halbritter K, Rastan A, Schellong S. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. J Vasc Surg. 2010 Nov;52\(5\):1246-50.](#)

Objectives: To test the hypothesis that, "that a 10-day course of therapeutic low-molecular-weight heparin (LMWH) could be superior to compression therapy alone." (p. 1246)

Methods: This prospective, open-label, randomized controlled trial was conducted at the University of Dresden Medical School. Consecutive patients with symptomatic, sonographically proven isolated calf muscle vein thrombosis were included (gastrocnemius or soleal veins only), if symptom onset was < 14 days prior to diagnosis. Patients with DVT in the peroneal or tibial veins, proximal DVT, PE, prior calf vein thrombosis, heparin hypersensitivity, creatinine > 180 micromol/L, malignant hypertension, active bleeding, cerebral hemorrhage, recent brain/spinal/ophthalmologic surgery, fibrinolysis in the last 24 hours, active peptic ulcer disease, acute bacterial endocarditis, familial bleeding disorder, any other indication for anticoagulation, a life expectancy < 3 months, of age < 8 years were excluded from the study.

Patients were randomized in blocks of 10 to receive either nadroparin (180 antiXa u/kg) for 10 days plus compression therapy for 3 months (LMWH group), or compression therapy alone for 3 months. Patients were followed by clinical and ultrasound examinations at day 3, days 10-12, 4 weeks, and 3 months.

The primary outcome was the development of sonographically proven progression of clot into the deep veins (defined as incompressibility of previously unaffected segments of the popliteal, posterior tibial, or peroneal veins) or PE diagnosed by objective testing. Secondary outcomes included:

- 1) major bleeding (defined as a drop in hemoglobin > 2 mmol/L, transfusion of two units of packed red blood cells, or retroperitoneal, joint, or cerebral bleeding).
- 2) Death not due to PE.
- 3) Complete sonographically proven recanalization of the involved vein.

A total of 109 patients were enrolled in the study; 55 were randomized to the LMWH group and 54 to compression therapy alone. One patient in each group dropped out,

leaving 54 and 53 patients in the two groups, respectively. The mean age was 55 years and 63% were female.

Guide		Comments
I.	Are the results valid?	
A.	Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?	
1.	Were patients randomized?	Yes, although the method of randomization and sequence generation was in no way described (aside from the use of block randomization).
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be “randomized” to a particular group?	Uncertain. As the authors do not provide any information regarding the randomization process, it is impossible to know if randomization was concealed, or if the process could be easily subverted (allocation concealment).
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain. The authors do not mention any crossover between the two groups. It is uncertain whether or not all patients in the LMWH group actually received nadroparin, or if any patients in the compression only group received some form of anticoagulation. Presumably, an intention to treat analysis was performed.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to gender, age, location of thrombosis (soleal vs. gastrocnemius veins), and most risk factors for DVT. Patients in the compression only group were much more likely to have undergone surgery or suffered some form of trauma compared (47% VS. 20%, respectively; p = 0.03).
B.	Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?	
1.	Were patients aware of group allocation?	Yes. This was an unblinded study, although it seems unlikely that performance bias on the part of patients would influence outcomes.
2.	Were clinicians aware of group allocation?	Yes. This was an unblinded study, although it seems unlikely that performance bias on the part of clinicians would influence outcomes.
3.	Were outcome assessors aware of group allocation?	This was an unblinded study, and it is possible the knowledge of treatment group could have affected

		the interpretation of follow-up ultrasounds (observer bias).
4.	Was follow-up complete?	No. One patient in each group failed to follow-up. This study therefore had excellent follow-up.
II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	<ul style="list-style-type: none"> The primary outcome (progression into deep veins) occurred in two patients in each group (3.7% vs. 3.8% in the LMWH and compression-only groups, respectively), for a relative risk (RR) of 0.98 (95% CI 0.14-6.7). No clinical PE, death, or major bleeding event occurred in either group. No recurrent isolated distal DVT was seen in either group. Thrombus recanalization was seen in 66% of patients in the LMWH group and 60% of patients in the compression-only group.
2.	How precise was the estimate of the treatment effect?	See above. This was a small study with very wide confidence intervals, raising the possibility of a Type II error.
III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Uncertain. Aside from the obvious difference in nationality, the authors provide very little information regarding the patients enrolled, including method of identification, location of enrollment, and medical comorbidities. It should be noted that this study included ONLY patients with isolated calf muscle DVTs (soleus and gastrocnemius) and did not include patients with peroneal and tibial thromboses.
2.	Were all clinically important outcomes considered?	Mostly yes. The primary outcome is sensible, and the study addresses the primary complications associated with treating and not treating distal DVTs.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study does seem to suggest that there is no benefit to treating isolated calf muscle DVTs, but generalizability of the results are difficult owing to small sample size, lack of proper reporting, and lack of study blinding.

Limitations:

1. The authors failed to adhere to [CONSORT guidelines](#) for the reporting of trials.
 - a. There is no description of how patients were randomized, how the [randomization sequence was generated](#), or what (if any) measures were used to ensure [allocation concealment](#).
 - b. The authors provide no study dates to let us know when patients were enrolled.
 - c. There is no flow chart depicting eligible vs. enrolled patients, and no assessment of whether patients were eligible but not enrolled were similar to those who were enrolled.
 - d. The authors do not mention if there was any allocation crossover or make any assessment of adherence to the treatment, nor do they specify that an [intention to treat analysis](#) was used.
 - e. There is very little information regarding demographics or medical comorbidities.
2. The patients, clinicians, and investigators were not blinded to group allocation, raising the possibility of [performance bias](#).

Bottom Line:

This small, reportedly randomized controlled trial evaluating the treatment of isolated calf muscle DVTs demonstrated no difference in outcomes between patients treated with LMWH and those not anticoagulated. It is difficult to draw conclusions from this study due to its small sample size, and its failure to adhere to reporting guidelines.