Critical Review Form
Therapy

PGY-1

HYPERLINK "http://pmid.us/27836513"Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol. 2016 Dec;3(12):e556-e562.

Objectives: **"to assess whether low-molecular-weight heparin led to better outcomes than placebo in outpatients with a first symptomatic calf DVT." (p. e557)**

Methods: **This randomized controlled trial was conducted at 23 centers in Canada, France, and Switzerland between February 1, 2008, and November 30, 2014. Adult patients (18 years or older) with a first, acute, symptomatic calf DVT confirmed by whole-leg compression ultrasonography were eligible for enrollment. Exclusion criteria were isolated superficial venous thrombosis, presence of a proximal DVT, pregnancy, previous documented venous thromboembolism, clinically suspected PE, active or recent malignancy, another indication for long-term anticoagulation, platelet count < 100K, impaired renal function, known hypersensitivity to heparin, active bleeding or high risk of bleeding, bodyweight > 115 kg or < 40 kg, daily NSAID use (except aspirin < 160 mg/day), ongoing requirement for thromboprophylaxis, previous receipt of therapeutic anticoagulation for more than 2 days, or enrollment in another trial in the previous 30 days.**

Patients were randomized in a 1:1 fashion to receive nadroparin (171 UI/kg daily) or placebo administered by the patient for 42 days. Patients were scheduled to follow-up in-person at days 3-7 and at day 42. Follow-up visits included bilateral whole-leg compression ultrasonography. Patients found to have a recurrent, symptomatic thromboembolic event were removed from the study and treated with anticoagulation. A final telephone follow-up visit was performed at 90 days. The primary outcome was a composite outcome of extension of the calf DVT into the proximal veins, a contralateral proximal DVT, or symptomatic PE by day 42. Secondary outcomes included each component of the primary outcome at day 42 and day 90, major bleeding or clinically relevant non-major bleeding at day 42 and day 90, death and serious adverse events at day 42 and day 90, and post-thrombotic syndrome and quality of life at 1 year.

Out of 746 patients screened during the study period, 259 were enrolled. There were 126 patients randomized to receive nadroparin and 133 to receive placebo. After losses to follow-up and withdrawal of consent, there were 122 patients in the nadroparin group and 130 in the placebo group in the modified intention-to-treat analysis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to receive nadroparin or placebo.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Random allocation of each patient was centrally determined by an independent research clinical centre using the ORTA/VISTA software of the European Organisation for Research and Treatment of Cancer (EORTC) and its web interface, with allocation stratified by study centre. Variable block sizes were used. Sequentially numbered boxes including 42 syringes were delivered to the pharmacy of the enrolling centres. All boxes were tamper-proof, equal in weight, and similar in appearance. Using an EORTC web-based interface, the investigator received by email the number of the box that had to be delivered to the patient." (p. e558)
3.	Were patients analyzed in the groups to which they were randomized?	Mostly yes. "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)." (pp. e558-e559)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patents were mostly similar with respect to age, gender, location of DVT (vein(s) involved), risk factors, and concomitant medication use.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "All study personnel, participants, and outcome assessors (central adjudication committee) were masked to group assignment." (p. e558)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	No. See above.
4.	Was follow-up complete?	Yes. Out of 259 patients randomized, only 7 (2.7%) were lost to follow-up or withdrew consent. Similar numbers were lost to follow-up in each group.

II.	What are the results ?	

1.	How large was the treatment effect?	• The primary composite outcome occurred by day 42 with similar frequency in the nadroparin (3%) and placebo (5%) groups: Risk difference -2.1%, 95% CI -7.8% to 3.5%.
		  ○ Proximal extension of the DVT was less common in the nadroparin group (1.6%) than the placebo group (5.4%), though this difference was not statistically significant.
		  ○ A pulmonary embolism occurred slightly more frequently in the nadroparin group (1.6%) than the placebo group (0%), though this difference was not statistically significant.
		  ○ No difference was seen in subgroups with an isolated muscular calf DVT (gastrocnemius or soleus vein) and those with a peroneal or posterior tibial vein DVT, or in a per protocol analysis.
		• The primary composite outcome occurred by day 90 with similar frequency in the nadroparin (3.3%) and placebo (6.2%) groups: risk difference -2.9%, 95% CI -8.7% to 2.8%.
		• Major or clinically relevant non-major bleeding occurred more frequently in the nadroparin group (4%) than the placebo group (0%): risk difference 4.1%, 95% CI 0.4 to 9.2%.
		• One death occurred in the study in a patient in the nadroparin group but was related to metastatic pancreatic cancer diagnosed after enrollment in the study.

2.	How precise was the estimate of the treatment effect?	See above. The confidence intervals were fairly narrow, despite early termination of the study.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Somewhat. While this study was conducted outside of the US with potential ethnic and medical differences to our patient population, the study included non-cancer patients only with strict inclusion criteria. The prognosis for this patient population would likely be similar to our patient population. Due to the nature of the study, early access to repeat venous compression ultrasonography was readily available to assess for proximal DVT extension; lack of insurance or access to follow-up may preclude this in many of our patients. Additionally, nadroparin (a LMWH) was

		used for anticoagulation, where most patients we diagnose with DVT are now initiated on a direct oral anticoagulant (DOAC) such as apixaban.
2.	Were all clinically important outcomes considered?	Yes. While the primary composite outcome is somewhat problematic, the authors considered short- and longer-term extension of the DVT into the proximal veins, development of a PE, death, and bleeding complications. They plan to report 1-yer quality of life scores and post-thrombotic syndrome results at a later date.
3.	Are the likely treatment benefits worth the potential harm and costs?	Likely no. While there was a trend toward increased incidence of extension of thrombosis into the proximal veins with placebo use, there was also a trend towards higher rates of PE development with nadroparin use. As management of proximal DVT extension alone would only require anticoagulation initiation, without apparent risk of more severe consequences, it seems reasonable to withhold anticoagulation for calf DVT in appropriate patients with adequate access to follow-up compression ultrasonography.

Limitations:

1. **The study was stopped early due to expiration of the study drug, with 259 of the planned 572 patients.**

2. **The primary outcome assessed was a composite outcome whose individual components (i.e. PE vs proximal DVT) are not necessarily of equal importance.**

3. **Patients in the treatment arm in this study were treated with intramuscular nadroparin; standard therapy for DVTs is now direct oral anticoagulants, which could potentially affect the proportion of patients with the outcomes being assessed (external validity).**

Bottom Line:

This multicenter, randomized controlled trial comparing management of isolated calf DVT with placebo vs. intramuscular nadroparin for 6 weeks found no statistically significant different the primary composite outcome of extension of the calf DVT into the proximal veins, a contralateral proximal DVT, or symptomatic PE by day (risk difference -2.1%, 95% CI -7.8% to 3.5%). While there was a trend toward increased rates of proximal DVT development in the placebo group, there was a slightly higher rate of PE in the nadroparin group.