Critical Review Form
Therapy

Horner D, Hogg K, Body R, Nash MJ, Baglin T, Mackway-Jones K. The anticoagulation of calf thrombosis (ACT) project: results from the randomized controlled external pilot trial. Chest. 2014 Dec;146(6):1468-77.

Objectives: **"to establish the feasibility of a definitive trial...to define the incidence of IDDVT [isolated distal DVT] in ambulatory patients and to evaluate recruitment and compliance to trial protocol..." and "to assess clinically relevant complication rates in patients treated with or without anticoagulation." (p. 1469)**

Methods: **This pilot randomized, controlled trial was conducted during a consecutive 16-month period in 2011 and 2012 at the Central Manchester University Hospital in Manchester, UK. Patients aged > 16 years diagnosed with an IDDVT following whole-leg compression ultrasound were eligible for inclusion. Exclusion criteria included hospitalized patients, patients already on long-term anticoagulation or with other indication for anticoagulation, proximal DVT or PE, active bleeding, recent hemorrhagic CVA or GI bleed, pregnancy, and presence of chronic thrombus on prior US.**

Patients were randomized via a web-based platform in permuted block sizes in a 1:1 ratio to either 3 months of anticoagulation or conservative management. Patients in the anticoagulation group received subcutaneous dalteparin initially, with a phased transition to warfarin, with a goal INR of 2.5 (2.0-3.0). Patients in the control group were treated with anti-inflammatory medication and paracetamol (acetaminophen). Patients in both groups were fitted for compression stockings.

Follow-up included repeat compression ultrasonography on days 7 and 21 by an ultrasonographer blinded to group allocation, as well as telephone follow-up at 90 days using a standardized data collection template. Any patient with propagation of the DVT to the level of the popliteal trifurcation, or who developed a PE, was immediately started on anticoagulation.

The primary clinical outcome was "serious thromboembolic complication," defined as proximal propagation, symptomatic PE, VTE-related sudden death, or major bleeding.

Out of 951 patients with suspected DVT, 93 were diagnosed with IDDVT, of whom 79 were eligible for the trial and 70 gave consent and were enrolled. Mean age in the treatment and control groups was 60.9 years and 59.8 years, respectively, and 74.3% and 57.1% were female in each group.

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. Patients were randomized using permuted blocks in a 1:1 fashion to receive either anticoagulation with a vitamin K antagonist or antiinflammatory medication.
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?	Yes. "Randomization occurred via a web-based platform (www.sealedenvelope.com) with an externally generated randomization sequence in variable permuted block sizes...Randomization occurred following written informed consent, such that allocation concealment was maintained until the absolute point of inclusion." (p. 1469)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The authors specifically note that analysis was by intention to treat. Crossover occurred in 13 patients in the control group (37.1%) and two patients in the intervention group (5.7%). In the control group, crossover occurred due to patients achieving the primary outcome (n = 4), patient request (n = 1), anticoagulation during hospital admission for other reasons (n = 6), and anticoagulation initiation in the community (n = 2).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to age and gender. Somewhat more patients in the therapeutic group had "provoked" IDDVTs (68.8% vs. 54.3), with many more having undergone recent surgery (34.3% vs. 14.3%). Given the small number of patients in the study, differences in percentages may not be statistically significant.
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?	No. "All patients, regardless of allocation, underwent sequential repeat whole-leg compression ultrasound imaging on days 7 and 21, performed by an accredited vascular sonographer blinded to treatment allocation." (p. 1469). This limits the possibility of observer bias.
4.	Was follow-up complete?	No, though it was pretty good. There were 5 patients lost to follow-up by day 7 (92.9% compliance), and another 5 lost by day 21 (85.7% compliance). Nine of the ten patients lost to f/u by day 21 were in the intervention group (attrition bias). Only one patient could not be contacted at 90 days.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• The primary outcome occurred in 4 patients in the control group (11.4%) and none in the treatment group, for an absolute risk reduction (ARR) of 11.4% (95% CI -1.5% to 26.7%). • No patients in either group had any major bleeding. • Minor bleeding occurred in 3 patients in the control group (8.6%) and 7 patients in the treatment group (20%), for an ARR of -11.4% (95% CI -29.7% to 7.1%).
2.	How precise was the estimate of the treatment effect?	See above. Due the small sample size in this pilot study, 95% CI's crossed unity for all outcomes.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Likely yes. Although this study was performed in the UK, where the national healthcare system allows better follow-up, these were patients with isolated calf DVTs diagnosed in the ED of a university-affiliated hospital. It seems likely that the risks and benefits of anticoagulation would be similar in our patient population.
2.	Were all clinically important outcomes considered?	Yes. The primary outcome was a sensible one, comprising a composite of proximal clot propagation and development of PE. The authors also evaluated bleeding risk and

		adverse events (which included hospital readmission rates). They did not evaluate cost, quality of life, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a pilot study meant to primarily demonstrate the feasibility of a larger randomized control, and was not intended to change practice. While the study does at least suggest some possible benefit to anticoagulation in terms of reducing the risk of clot propagation and PE development, the results are limited by the small sample size, and hence did not achieve statistical significance. In addition, there was a bias in terms of larger loss to follow-up in the treatment group, as well as significant treatment crossover in the control group.

Limitations:

1. **There was a large degree of crossover in the control group, with over a third of these patients receiving therapeutic anticoagulation during the study period.**

2. **There was a fairly high risk of attrition bias, as 9 of 10 patients lost to follow-up were in the treatment group. It is possible that several of these patients achieved the primary outcome, and hence the study may overestimate the treatment effect.**

3. **The patients, clinicians, and investigators were not blinded to group allocation, raising the possibility of performance bias.**

4. **This was a small study intended as a pilot trial. As a result, the 95% confidence intervals are wide and cross unity for all the outcomes. It is easy to make a type II error in such cases. A larger study, which is underway, will provide much more useful results (study power).**

Bottom Line:

In this small, pilot trial evaluating the use of oral anticoagulation in the management of isolated distal DVTs, there was a trend toward a decrease in the composite outcome of clot propagation into the popliteal vein and development of PE. While this outcome did not achieve statistical significance, this was a pilot trial and was not intended to change management. The larger trial underway will need to overcome several hurdles seen in this study, including a bias toward loss to follow-up in the treatment group and large amount of treatment crossover in the control group.