> ## Critical Review Form
> ## Therapy
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> Utter GH, Dhillon TS, Salcedo ES, Shouldice DJ, Reynolds CL, Humphries MD, White RH. Therapeutic Anticoagulation for Isolated Calf Deep Vein Thrombosis. JAMA Surg. 2016 Jul 20:e161770.

Objectives: "to evaluate whether therapeutic anticoagulation at our center might be associated with reduced likelihood of proximal DVT or PE.

Methods: This retrospective cohort study was performed at the University of California, Davis, Medical Center in Sacramento from January 1, 2010 to December 31, 2013. All patients aged 18 years or older with a first isolated calf DVT during the study period (defined as involving 1 or more veins distal to the popliteal vein) were eligible for inclusion. Exclusion criteria were chronic DVT, PE or DVT diagnosed within 180 days prior to the calf DVT diagnosis, radiographically confirmed PE at the time of calf DVT diagnosis, an enduring contraindication to anticoagulation, or if the patient was already undergoing therapeutic anticoagulation at the time of DVT diagnosis.

Data was collected from the electronic medical record by one investigator using a standardized abstraction instrument. The exposure under investigation was the intention to treat the isolated calf DVT with therapeutic anticoagulation, including use of therapeutic doses of unfractionated heparin, low-molecular-weight heparin (LMWH), a factor Xa inhibitor, warfarin, or a direct thrombin inhibitor. A sensitivity analysis was performed to assess actual therapeutic effect, but the primary analysis was intention to treat.

The primary outcome was radiographically confirmed proximal DVT or PE within 180 days. Secondary outcomes included bleeding episodes, death, and a composite outcome of proximal DVT, PE, or death.

Out of 14,056 lower extremity duplex studies performed the study period, 973 were found to have an isolated calf DVT, out of which there were 697 unique patients. Of these, 313 met exclusion criteria, leaving 384 patients in the analysis. Physicians planned to treat 243 of these (63%) with therapeutic anticoagulation. This consisted of warfarin in 182 patients (75.2%), a low molecular-weight heparin in 43 (17.7%), continuous IV heparin in 15 (6.2%), and rivaroxaban and bivalirudin in 1 case each (0.4%).

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?	No. This was a retrospective, observational study in which the decision to administer anticoagulants was made at the discretion of the treating clinician based on clinical factors. There is a therefore a high risk of selection bias, and a high likelihood that patients will not be balanced with respect to known and unknown confounding factors.
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?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed based on whether or not the clinician intended to initiate anticoagulation (intention to treat analysis). Two patients where initially intended not to receive anticoagulation were placed on therapeutic anticoagulation, while one patient intended to receive anticoagulation did not receive anticoagulation. These patients were analyzed according to the plan that was initially intended.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Lack of randomization resulted in significant imbalances in certain prognostic factors. Patients intended to receive anticoagulation were far more likely to have an acute medical illness (58.7% vs. 45.5%) and to be on exogenous estrogen (7.4% vs. 1.4%). On the other hand, patients in the control group were more likely to have had surgery in the preceding 30 days (44.7% vs. 34.6%), to have had a traumatic injury in the preceding 30 days (24.8% vs. 15.3%), or to have a nonambulatory status (40.4% vs. 28.0%); they were also more likely to have received prophyactic anticoagulation in the 7 days before calf DVT diagnosis (44.7% vs. 27.6%).
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 a nonrandomized study and the decision to begin anticoagulation was at the discretion of the treating clinician. It seems unlikely that performance bias on the part of the patients would affect the outcomes.
2.	Were clinicians aware of group allocation?	Yes. This was a nonrandomized study and the decision to begin anticoagulation was at the discretion of the treating clinician. It seems quite possible that performance bias on the part of the clinicians would affect the outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. While most of the outcomes were fairly objective, neither clinicians, radiologists, nor ultrasonographers were blinded to group allocation. It is possible that some degree of observer bias could have affected the outcome. It is also quite possible that the decision to perform subsequent imaging would be influenced by the use of anticoagulation.
4.	Was follow-up complete?	Uncertain. This was a retrospective cohort study, and follow-up was limited to information located in the electronic medical record at the study hospital. Subsequent visits to outside hospitals and undiagnosed events would not have been captured by this methodology. Less than half of patients underwent repeat testing for propagation of DVT; this was more likely to occur in the control group than in the treatment group (53.2% vs. 39.3%), biasing the results in favor of the treatment group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Proximal DVT occurred more frequently in the control group than the treatment group, though this did not achieve statistical significance: 5.0% vs. 1.6%, unadjusted RR 0.33 (95% CI 0.10-1.11). • PE occurred also occurred more frequently in the control, though this also did not achieve statistical significance: RR 0.39 (95% CI 0.11-1.35). • The composite outcome of proximal DVT or PE occurred more frequently in the control group, and did achieve statistical significance: 9.2% vs. 3.3%, RR 0.36 (95% CI 0.15 to 0.84).

		• After statistical adjustment for age, sex, care setting, existing cancer, and history of DVT or PE, this treatment benefit persisted: adjusted OR 0.33 (95% CI 0.12 to 0.87). • Clinically significant bleeding was more common in the treatment compared to the control group: 8.6% vs. 2.2%, unadjusted OR 4.35 (95% CI 1.27 to 14.9), adjusted OR 4.87 (95% CI 1.37 to 17.3).
2.	How precise was the estimate of the treatment effect?	See above. The results for the primary composite outcome and for bleeding did achieve statistical significant both before and after adjustment for confounding variables.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Not really. Few of the patients in the study were ED patients (3.4%). The majority were inpatients following recent surgery or trauma, and a large percent were nonambulatory. It seems likely that clot propagation would be less likely in our mostly ambulatory population, likely reducing any benefit to anticoagulation.
2.	Were all clinically important outcomes considered?	Mostly. The authors considered the most clinically important outcomes in their analysis (clot propagation, PE, bleeding), but they did not asses cost, hospital length of stay for admitted patients, quality of life, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a retrospective cohort study subject to the inherent biases of such studies, and should not be used to change management. While this study suggests some benefit to anticoagulation for calf DVT in a largely inpatient setting, this benefit must be weighted against the large increase in bleeding risk. Further randomized controlled trials will need to be conducted to conclude whether benefits outweigh risk. Additionally, studies should be completed in the outpatient setting to see if there is any benefit in these patients.

Limitations:

1. This was a retrospective, observational study at high risk of **selection bias**, and with a high likelihood that patients will not be balanced with respect to known and **unknown confounding factors**.

2. Less than half of patients underwent repeat testing for propagation of DVT; this was more likely to occur in the control group than in the treatment group (53.2% vs. 39.3%), biasing the results in favor of the treatment group.

3. Over half of the patients in this study were inpatients, many following recent surgery or trauma, and many with a nonambulatory status. Is seems likely that clot propagation would be more likely in such patients compared to ambulatory patients seen in the ED (**external validity**).

4. This was a retrospective cohort study, and follow-up was limited to information located in the electronic medical record at the study hospital. Subsequent visits to outside hospitals and undiagnosed events would not have been captured by this methodology.

Bottom Line:

This retrospective cohort study suggests some benefit to anticoagulation for calf DVT (adjusted OR 0.33l 95% CI 0.12 to 0.87) in a largely inpatient setting accompanied by a large increase in bleeding risk (adjusted OR 4.87; 95% CI 1.37 to 17.3). Further randomized controlled trials will need to be conducted to conclude whether benefits truly outweigh risk. Additionally, studies should be completed in the outpatient setting to see if there is any benefit in these patients.