

In low-risk patients with isolated calf DVT (IDDVT), what is the morbidity risk of treating with repeat ultrasound/observation versus anticoagulation?

Discussion Leader: Doug Bias, M.D.

Clinical Scenario:

A 42-year-old woman presents to the ED with the chief complaint of left leg swelling. She recently underwent surgery for a left ankle fracture 4 weeks ago. Over the last day or two she has had significantly increased leg swelling and more recently reports some dull pain in the affected leg. She denies chest pain, shortness of breath, or cough. On physical examination, her respiratory exam is unremarkable, and her left leg is 2 cm greater in circumference than her right, with mild pitting edema in the left leg only. The edema does not encompass the entire left leg. There is no tenderness to palpation of the popliteal fossa or medial thigh and there are no visibly engorged collateral veins. The patient's past medical history includes well-controlled hypertension but she is otherwise healthy. Ultrasound reveals posterior tibial and peroneal vein DVTs. You remember hearing some debate about treating "below-the-knee DVTs" and wonder if you should treat this with anticoagulants and their risk for bleeding or can a more conservative approach without the bleeding risk be as beneficial?

Primary Article for Discussion:

Righini M et al. "Anticoagulant Therapy for Symptomatic Calf Deep Vein Thrombosis (CACTUS): A Randomised, Double-Blind, Placebo-Controlled Trial." *Lancet Haematol* 2016. S2352 – 3026 (16): 30131 – 4.

Articles pertaining to particular morbidity questions:

Risk for Pulmonary Embolism with IDDVT?:

Wu A. R., Garry J., Labropoulos N. "Incidence of pulmonary embolism in patients with isolated calf deep vein thrombosis." *J Vasc Surg Venous Lymphat Disord*. 2017 Mar;5(2):274-279. doi: 10.1016/j.jvsv.2016.09.005. Epub 2016 Dec 14.

Utter G. H., Dhillon T. S., Salcedo E. S., Shouldice D. J., Reynolds C. L., Humphries M. D., White R. H. "Therapeutic Anticoagulation for Isolated Calf Deep Vein Thrombosis." *JAMA Surg*. 2016 Sep 21;151(9):e161770. doi: 10.1001/jamasurg.2016.1770. Epub 2016 Sep 21. PMID: 27437827

Risk for extension with IDDVT?:

Utter G. H., Dhillon T. S., Salcedo E. S., Shouldice D. J., Reynolds C. L., Humphries M. D., White R. H. "Therapeutic Anticoagulation for Isolated Calf Deep Vein Thrombosis." *JAMA Surg.* 2016 Sep 21;151(9):e161770. doi: 10.1001/jamasurg.2016.1770. Epub 2016 Sep 21. PMID: 27437827

Risk for Post-thrombotic Syndrome (PTS) with IDVT?:

Kahn, S. R., et al. "Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis." *Annals Of Internal Medicine.* 149 (10), 2008 Nov 18, pp. 698-707

Baldwin M. J., Moore H. M., Rudarakanchana N., Gohel M., Davies A. H. "Post-thrombotic syndrome: a clinical review." *J Thromb Haemost.* 2013 May;11(5):795-805

Tick L. W., Kramer M. H., Rosendaal F. R., Faber W. R., Doggen C. J. "Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis." *J Thromb Haemost.* 2008 Dec;6(12):2075-81.

Risk for recurrence?:

Galanaud J. P., Sevestre M. A., Genty C., et al. "Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis." *J Thromb Haemost* 2014; 12: 436–43.

Guidelines:

Kearon C, Akl E, Ornelas J, et al. "Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report." *Chest.* 2016;149(2):315-352.

Journal Club Discussion:

Prior to journal club, I had asked everyone to read the primary article, which was a recent article that made the rounds in the FOAM Ed realm. I also asked them to choose one of four particular morbidities/sequelae associated with DVTs and read the associated articles. Journal club began with discussion of the first article. This was an underpowered study that gives very little guidance on how to treat distal calf DVTs; however, as would be expected, there was more risk for bleeding in the anticoagulation group. We compared this article with the clinical guidelines presented in the journal CHEST. These guidelines do suggest that patients who are low-risk with symptomatic calf DVT can safely be managed with serial ultrasound

testing without anticoagulation. As there is no clear optimal approach at this time, the general consensus was to advocate for a shared decision-making strategy regarding the use of anticoagulation vs no anticoagulation in isolated low-risk, distal DVTs. With either of these strategies, close follow up with repeat ultrasound should be performed to assist with further management and treatment decisions. We also looked at and discussed the evidence surrounding various morbidities/sequelae, as summarized below:

Tanner Weigand's summary of the articles looking at risk for PE with IDDVT (the second article also looks at the risk for IDDVT extension):

Article #1: "Incidence of pulmonary embolism in patients with isolated calf deep vein thrombosis." Journal of Vascular Surgery: Venous and Lymphatic Disorders" by Wu et al.

Background: The true incidence of and severity of PE secondary to isolated calf DVT has not been well defined or studied. This has made the topic of treatment for isolated calf DVTs somewhat controversial. The most recent CHEST guidelines recommend those with distal DVT without severe symptoms or risk factor for extension be observed with serial imaging over 2 weeks instead of anticoagulation but this is a Grade 2C recommendation. In those that have severe symptoms or risk factors for extension the recommendation is for anticoagulation over serial imaging which is again a Grade 2C recommendation. For this study, calf DVT or distal DVT include DVTs distal to the popliteal vein.

What they did: This was a meta-analysis to look at PE frequency and severity of PE in those with isolated calf DVT. Two electronic databases (Medline and Scopus) were used to find studies on which occurrence of PE in patients with distal DVT were investigated.

Outcomes: Incidence of pulmonary embolism detected after initial diagnosis of proximal calf DVT

Inclusion: Included studies were those in which occurrence of PE in patients with symptomatic or asymptomatic isolated calf DVT were investigated.

Exclusion: Studies in which patients had combined proximal and distal DVTs, concurrent PE at time of distal DVT diagnosis, and any retrospective study design that did not allow for determination of isolated calf DVT and PE as separate events.

Results: 21 total papers met inclusion criteria for examination. Eight of these were randomized trials and 13 were prospective cohort studies. The incidence of PE in those with isolated calf DVT ranged from 0 to 6.2%.

Discussion: While this is an interesting meta-analysis we must keep in mind that many of the studies were prospective in nature. While there was patient heterogeneity, the methods of PE detection was quite different among the studies. For example, the surveillance methods used

to detect PE were not consistent. The V/Q scan was most commonly used to diagnose PE among the studies and was used for 10 of the studies which demonstrated a range of detection of 0 to 6.2%. Three of the studies used CTA to detect PE with range of detection from 0 to 3.4%. What is very important to note here is that patients investigated for PE were almost exclusively those that were symptomatic. Only 3/21 of the studies used serial objective scanning at study inclusion and designated follow up. Thus, there is potential for a large group of patients that had asymptomatic PEs that were never diagnosed. This opens up an entire different discussion that we don't have time for but there are some studies that suggest those with silent PE's have increased potential to progress to symptomatic PEs within 15 days of anticoagulation therapy.

However, there are also arguments that small PEs should be left untreated. With respect to positives, the study did a nice job excluding those with concurrent proximal DVTs or those with concurrent diagnosis of PE on initial diagnosis of the proximal DVT. However, getting back to the previous point, only patients that were symptomatic were generally scanned for PE detection so how many concurrent asymptomatic PE's with calf DVT is unclear.

Bottom line: This study is certainly thought provoking with respect to what is the true risk of PE from isolated calf DVT. With that being said, the variability in detection and clinical significance of PE's in these patients remains uncertain. More studies are needed to guide treatment guidelines.

Article # 2: "Therapeutic Anticoagulation for Isolated Calf Deep Vein Thrombosis." JAMA surgery by Utter et al.

Background: Nearly half of all DVTs diagnosed by ultrasound are isolated calf DVTs. The clinical significance of isolated calf DVTs is not entirely certain and the appropriate treatment for these DVTs is still uncertain. Despite recent CHEST guidelines, the body of evidence supporting to treat or not to treat isolated calf DVTs is lacking. Concerns that arise from isolated calf DVT are the risk for proximal extension as well as risk of PE.

What they did: This was a single centered retrospective cohort study at UC Davis that evaluated patients with isolated calf DVT and, through chart reviews, searched for patients that received intended anticoagulation treatment for the DVT vs those that were not provided with intended anticoagulation treatment. They then divided these patients into separate groups and evaluated them for propagation of DVTs and PEs.

Outcomes: Primary outcome was defined as radiographically confirmed proximal DVT or PE occurring within 180 days. Secondary outcomes included bleeding episodes (clinically significant), death, and a composite of proximal DVT, PE, or death.

Inclusion: Patients with acute, isolated calf DVT.

Exclusion: Patients with concurrent proximal DVT or PE diagnosed within 180 days prior to calf DVT diagnosis, those with chronic calf DVTs, patients with an enduring contraindication to

anticoagulation existed, or patients who were already receiving anticoagulation at time of diagnosis.

Results: Of those that met all criteria for inclusion without exclusion criteria 384 patients were used for analysis- 243 in which physicians intended to treat the calf DVT with anticoagulants and 141 patients in which the calf DVT was not intended to be given therapeutic anticoagulation

Treatment. This is where the data becomes a little tricky. Of the initial 141 control patients 83 (59.0%) and 172 of the treated group (71.0%) last had an interaction at a healthcare center at least 180 days after diagnosis of calf DVT. In the control group 53/141 (53.2%) underwent duplex ultrasound study within 180 days of distal DVT diagnosis vs 95/242 (39.3%). In the control group, 28/141 (19.9%) had a PE study done within 180 days of diagnosis vs 46/242 (19.0%) in the treatment group. All except for 5 had CTA to evaluate for PE. A proximal DVT occurred in 7/141 (5.0%) in the control group and 4/242 (1.6%) in the treatment group. Pulmonary embolism occurred in 6/141 in the control group and 4/242 in the treatment group. Clinically significant bleeding occurred in 21/242 in treatment group vs 3/141 in the control group. Death occurred in 20/141 of control group patients and 28/242 of treatment group patients. So overall, therapeutic anticoagulation was associated with a decreased risk for proximal DVT or PE at 180 days (OR 0.33) but an increased risk for bleeding (OR 4.35).

Discussion: This study seems to agree somewhat with the most recent CHEST guidelines for anticoagulation of calf DVT's. On the surface it seems this study suggests to strongly consider anticoagulation on all distal DVT's which would be opposite of the CHEST guidelines but a closer look shows that most patient's diagnosed had >1 symptom as well as physical exam findings to go along with diagnosis of the calf DVT. Now the study didn't say this outright but perhaps these patients could be considered "severely symptomatic" and per the CHEST guidelines should receive anticoagulation. Another item that needs addressed is that the follow up scanning for proximal DVTs and PEs was not standardized which makes it uncertain exactly which patients were diagnosed with PEs. Were these severely symptomatic patients? And how many silent PEs could have been missed? These questions remain unanswered within this study. The other obvious weakness with the study is that it is retrospective and single centered. Despite weaknesses the results definitely compels one to strongly consider anticoagulation on isolated calf DVT given the non-trivial risk for proximal DVT or PE extension. The study also shines light on considering the risk factors of anticoagulation – especially the risk for bleeding. And with respect to anticoagulants, the anticoagulants used in the treatment group were not standardized and 81/141 control group patients received prophylactic anticoagulation after initial DVT diagnosis just to cloud the picture even more.

Bottom line: This study suggests anticoagulating isolated calf DVT's to prevent proximal DVT extension or PE. However, there are several weaknesses within the study and also other studies with conflicting results to make us question the results of this study. The decision to anticoagulate these patients with isolated calf DVT is certainly clear as mud.

Angela Palitto's summary of Post-Thrombotic Syndrome and the risk of it with IDVT:

What is Post-thrombotic Syndrome?

- A chronic and frequent complication of acute proximal DVT
- Affects approximately 1/2 of patients within the first 1-2 years
- Results in significant disability and impaired quality of life, comparable to lung disease, diabetes, arthritis and even CHF and cancer
- Acute DVT causes partial or complete obstruction of venous outflow
- Recanalization – process by which the thrombus undergoes changes in size, shape, and structure – leading to the lumen to be re-established
- Both the inflammatory response to the acute DVT and the process of recanalization cause direct damage to the venous valves, resulting in reflux
- Reflux and obstruction together results in progressive calf muscle pump dysfunction and venous HTN => high pressures transmit to capillary beds => tissue edema, subcutaneous fibrosis, tissue hypoxia, ulceration
- Rapid resolution of thrombus could preserve valvular function
- During first 3 months – 50% reduction in thrombus, with re-canalization occurring as early as 6 weeks from diagnosis
- At 3 years, up to 50% of legs still have some residual thrombus causing at least partial obstruction
- Rate of re-canalization has been shown to be related to the initial size of the thrombus and the site --- with distal thrombi undergoing more rapid and complete resolution

Risk Factors for Developing PTS

- Recurrent ipsilateral DVT – 3-6 fold increase
 - Already compromised veins get even more damage
- Females, Obesity, varicose veins, possibly older age
- DVT Location – area of continuing research
 - Proximal (ileofemoral and femoropopliteal veins)
 - obstruction is usually above the profunda femoral vein – which impairs collateral flow
 - Greater risk of PTS than popliteal of below (1.3 fold increase)
 - Distal should not be discounted
 - 9-20% of below-knee DVTs propagate to proximal
 - > 20% later show symptoms of PTS
 - Lower incidence is based on the faster regression, re-canalization, and reduced rate of recurrence
 - Calf and popliteal DVTs were found to have similar risk in one of the studies