Ultrasonography May Help Guide Decisions to Discontinue Anticoagulation Therapy for Deep Venous Thrombosis

Prandoni P, Prins MH, Lensing AWA, et al; AESOPUS Investigators. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med 2009;150:577–85.

Study Overview

Objective. To determine whether the use of ultrasonography assessing for residual thrombosis can guide duration of anticoagulation in patients with a first presentation of symptomatic, proximal deep venous thrombosis (DVT).

Design. Randomized, multicenter, open-label trial.

Setting and participants. Outpatients aged ≥ 18 years with a first presentation of a proximal DVT were enrolled from 9 university or hospital centers in Italy between 1999 and 2003 if they had an initial uncomplicated course during 3 months of anticoagulation. Patients were excluded if they had a prior thromboembolism, cancer or a chronic underlying illness that caused immobility, a life-expectancy < 3 months, could not attend follow-up visits, had a diagnosed deficiency of natural anticoagulants or lupus-like anticoagulants based on laboratory testing performed prior to anticoagulation, needed anticoagulation for another indication (eg, atrial fibrillation, valve replacement surgery), or were pregnant. Secondary DVT was defined as DVT occurring in association with immobilization for > 7 days, recent (< 3 months) trauma, use of hormonal therapy, pregnancy, or surgery within 3 months prior to the DVT. All other DVT was defined as unprovoked.

Intervention. After 3 months of oral anticoagulant therapy, patients were randomly assigned to a fixed or flexible duration of warfarin therapy. In the fixed therapy group, patients with unprovoked DVT received 3 additional months of anticoagulation, whereas patients with secondary DVT discontinued treatment. In the flexible therapy group, treatment decisions were guided by residual thrombi on lower extremity venous ultrasonography. In the absence of residual thrombosis, anticoagulation was discontinued immediately. If residual thrombosis was found, anticoagulation was continued for up to 9 months in patients with an identified secondary cause of DVT or up to 21 months in patients with an unprovoked DVT. During flexible therapy, anticoagulation discontinuation was considered at standard intervals if ultrasonography showed no persistent thrombosis. Follow-up was scheduled at 3, 9, 15, 21, and 33 months for all patients.

Main outcome measures. Recurrent venous thromboembolism (VTE) up to 36 months after diagnosis of DVT, determined by surveillance ultrasonography or symptoms of thromboembolism on evaluation. Covariates included age, thrombophilic status (diagnosed with either factor V Leiden or prothrombin gene mutation), and whether the patient initially presented with signs or symptoms of pulmonary embolism. Secondary analyses included a stratified analysis by type of DVT (secondary or unprovoked) and major bleeding.

Main results. Of 1020 potentially eligible patients, 538 were randomized. 11.9% of patients in the flexible therapy group had recurrent VTE compared with 17.2% in the fixed therapy group (32 events in 270 patients vs. 46 events in 268 patients [adjusted hazard ratio {HR}, 0.64 [95% confidence interval {CI}, 0.39–0.99]). Results were similar but not significant when stratified by the cause of DVT (adjusted HR for unprovoked DVT, 0.61 [95% CI, 0.36–1.02]; adjusted HR for secondary DVT, 0.81 [95% CI, 0.32–2.06]). Death from any cause did not differ by group (11 patients on fixed therapy vs. 17 patients on flexible therapy; $P = 0.33$), and only 4 patients in the flexible therapy group and 2 in the fixed therapy group developed major bleeding complications (difference, 0.8 percentage points [95% CI, –1.0 to 2.5 percentage points]). In the multivariable analysis, predictors of recurrent DVT included history of thrombophilia and presentation with unprovoked DVT.

Conclusion. Anticoagulation therapy aided by ultrasonography to detect residual thrombosis in DVT decreased recurrent VTE.

Commentary

No treatment duration has been defined for DVT, especially if DVT is unprovoked. Recent guidelines have recommended at least 3 months of anticoagulation for DVT from identified secondary causes and extended-duration therapy for those with unprovoked DVT [1]. However, the exact meaning of "extended-duration" has varied widely in trials, from greater than 3 months to greater than 4 years. After

showing that residual thrombosis on ultrasonography was associated with a higher risk of recurrent VTE [2], Prandoni et al designed this trial to bring some clarity to the duration of DVT treatment and incorporated ultrasonography into a treatment algorithm for anticoagulation. The rate of recurrent VTE was lower among patients whose duration of anticoagulation was partly dependent on whether residual thrombosis was identified.

Another recent study of 258 patients with DVT found similar but attenuated results with a different research design [3]. Siragusa et al randomized 180 patients treated for 3 months for a first DVT and with evidence of residual thrombosis on ultrasonography to either therapy discontinuation or an additional 9 months of therapy. Prolonged therapy was associated with a nonsignificant reduction in recurrent thromboembolism up to 2 years after initial diagnosis. Additionally, therapy was discontinued in 78 patients with no residual thrombosis on ultrasonography at the time of enrollment (3 months after diagnosis), and only 1 patient experienced recurrence, a significant difference compared with those with residual thrombosis.

In this current study by Prandoni et al, compliance rates with follow-up ultrasonography were high, with more than 90% of patients in both arms completing the designated assessments. Approximately 10% of patients had alternations in the per-protocol anticoagulation courses because of subsequent events (ie, development of atrial fibrillation or cancer) or at the discretion of the patient's provider. However, all analyses were done as intention-to-treat.

Several limitations were apparent. The trial was not double-blinded because the use of ultrasonography to guide therapy required that both providers and patients be aware of testing results. Furthermore, the trial was underpowered to detect differences in the designated subgroups of patients with either unprovoked or secondary DVT. This lack of power to detect a difference is particularly disappointing for the subgroup with unprovoked DVT. The application of ultrasonography-guided therapy would be particularly helpful to resolve some of the uncertainty in treatment for this group. Further research should focus specifically on patients with unprovoked DVT.

It was not clear why the authors chose to exclude patients with a deficiency in a natural anticoagulant or the presence of a lupus-like anticoagulant while including patients with either factor V Leiden or prothrombin gene mutation. Inclusion of all patients, whether or not they have been diagnosed with a specific cause of an unprovoked DVT, would be more easily applicable to clinical practice, where testing for thrombophilia is often not undertaken until recurrence of thromboembolism. In fact, 2 recent systematic reviews found no randomized controlled trials or controlled clinical trials that investigated the benefits of testing for thrombophilia for prevention of recurrent VTE [4,5].

The frequent use of ultrasound in patients might be a challenge for clinical application as well. In the study, the protocol required ultrasonography at enrollment and every 6 months thereafter, up to 2 years after diagnosis if residual thrombosis was detected. If residual thrombosis was absent, then ultrasonography was discontinued. Perhaps less frequent ultrasounds in future protocols might be more realistic and improve the potential cost-effectiveness of the treatment protocol.

Ultimately, the rate of 11.9% for recurrent DVT is still quite high even in the ultrasonography-based treatment group, despite the improvements of this approach over usual care. Perhaps the addition of other promising diagnostic evaluations, such as the use of D-dimer to detect risk for recurrent VTE, might further improve the identification of patients who could safely discontinue anticoagulation [6].

Applications for Clinical Practice

Recurrence rates of VTE after a first DVT can be improved if treatment is partly based on the use of ultrasonography to detect residual thrombosis. Additional research must address whether the ultrasonography-based approach is helpful in patients with unprovoked DVT, a group at high risk for recurrence. Research must also employ combinations of strategies to determine who should be treated with prolonged anticoagulation.

—Review by Jason P. Block, MD, MPH

References

1. Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2007;146:204–10.
2. Prandoni P, Lensing AW, Prins MH, et al. Residual thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002;137:955–60.
3. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep venous thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. Blood 2008;112:511–5.
4. Cohn D, Vansenne F, de Borgie C, Middeldorp S. Thrombophilia testing for prevention of recurrent venous thromboembolism. Cochrane Database Syst Rev 2009;(1):CD007069.
5. Simpson E, Stevenson M, Rawdin A, et al. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness. Health Technol Assess 2009;13:iii, ix–x, 1–91.
6. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy [published erratum appears in N Engl J Med 2006;355:2797]. N Engl J Med 2006;355:1780–9.