CLINICAL UPDATE

Duration of anticoagulant therapy for deep-vein thrombosis

Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001;345:165-9.

Background: Recent clinical trials have shown a reduction in the rate of recurrent venous thromboembolism when the duration of anticoagulant therapy for idiopathic deep-vein thrombosis (DVT) (i.e., thrombophilic risk factors cannot be clearly identified) is extended past the traditional 3 months.[1,2] Whether this advantage is sustained after discontinuation of anticoagulant therapy is unknown.

Question: In patients with idiopathic DVT, what is the rate of recurrent venous thromboembolism after 3 and 12 months of anticoagulant therapy over 2 years of follow-up?

Study design: In this trial, conducted in 10 centres in Italy, 267 patients who had completed 3 months of warfarin therapy for a first episode of idiopathic proximal DVT were randomly assigned either to stop the therapy or to continue it for an additional 9 months. The warfarin dosage was adjusted to maintain an international normalized ratio of 2.0–3.0. In all cases, DVT had been confirmed by compression ultrasonography or venography and was considered idiopathic if it had occurred in the absence of prolonged (> 7 days) immobilization, recent (< 3 months) surgery or trauma, pregnancy, recent childbirth, oral contraceptive use or previously identified cancer or thrombophilia.

The primary outcome measure was the recurrence of venous thromboembolism over a follow-up period of at least 2 years. Bleeding was considered major if it led to a drop of at least 2 g/L in the hemoglobin concentration, required transfusion of 2 or more units of blood, occurred retroperitoneally or intracranially, or necessitated permanent discontinuation of the warfarin therapy. Although patients and treating physicians were not blinded to group allocation, all outcome events were assessed by an independent panel of adjudicators who were unaware of treatment assignment. Primary analysis was performed using the intention-to-treat principle.

Results: Baseline characteristics were comparable in the 2 groups. The mean age was 67.7 (standard deviation [SD] 7.3) years in the 3-month treatment group and 66.8 (SD 6.7) years in the 12-month treatment group. The proportion of men in the 2 groups was 54.5% and 61.2% respectively. Although the overall rates of recurrence were nearly identical in the 2 groups (15.8% and 15.7%, relative risk 0.99, 95% confidence interval 0.57–1.73), the mean time from randomization to recurrence was 11.2 months in the 3-month treatment group and 16.0 months in the 12-month treatment group. The rates of major bleeding in the 2 groups were 1.5% and 3.0% respectively. None of the recurrences or bleeding events was fatal.

Commentary: A previous trial[2] of longer-term anticoagulant therapy for idiopathic DVT was ended early when an interim analysis showed a significantly lower rate of recurrence among patients who continued the therapy beyond 3 months. The Italian trial, which completed the planned 9-month period of extended anticoagulant therapy, showed that the benefits associated with prolonged anticoagulation did not persist after the extended therapy was stopped, that is, recurrence was delayed but not prevented altogether. Although the lack of blinding renders this study vulnerable to detection bias, outcome events were evaluated objectively by an external group. If bias had come into play, an excess number of thromboembolic events might have been expected in the group given warfarin for 3 months; however, this was not the case.

Practice implications: Although accumulating evidence[1–3] supports the use of prolonged, perhaps even indefinite, anticoagulant therapy in patients with a first episode of idiopathic DVT, physicians must still weigh the risk of recurrent thromboembolism against the risk of significant bleeding in each case. Further research is needed to determine whether low-dose anticoagulant therapy, the use of newer agents with decreased bleeding risk or improvements in risk stratification can minimize both the recurrence of thromboembolism and the morbidity associated with long-term anticoagulant therapy in this patient population. — *Donald Farquhar*

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References

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