Review: Long-term anticoagulation reduces recurrent venous thromboembolism

Ost D, Tepper J, Mihara H, et al. **Duration of anticoagulation following venous thromboembolism: a meta-analysis.** JAMA. 2005;294:706-15.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hematol/Thrombo ★★★★★★☆ Pulmonology ★★★★★★☆

QUESTION

In patients with venous thromboembolism (VTE), does long-term anticoagulation reduce recurrence?

METHODS

Data sources: PubMed, EMBASE/Excerpta Medica Pharmacology, the Cochrane Central Register of Controlled Trials, and clinical trial Web sites of the U.S. government (www.clinicaltrials.gov) and GlaxoSmithKline (ctr.glaxowellcome.co.uk) (1969 to 2004).

Study selection and assessment: Randomized controlled trials (RCTs) that compared different durations of anticoagulation in patients with VTE, in which initial therapy was similar in both study groups after diagnosis, and recurrent VTE was assessed. Studies that enrolled only high-risk patients (such as protein S or C deficiency) were excluded. Study quality was assessed using the 5-point Jadad scale and a quality scale specific for VTE.

Outcomes: Incidence rates of recurrent VTE and major bleeding.

MAIN RESULTS

Analysis was based on a hypothetical model with 4 time points: At time A, VTE was diagnosed; at time B, patients were allocated to stop anticoagulation (i.e., received short-term anticoagulation) or to receive long-term anticoagulation; at time C, patients who were allocated to long-term anticoagulation had treatment stopped, but follow-up continued in both short- and long-term anticoagulation groups; and at time D, the study ended. The at-risk period to assess disease recurrence was from time B to D, long-term vs short-term anticoagulation was from time B to C, and additional follow-up was from time C to D.

15 RCTs (n = 5582) met the inclusion criteria. Study quality was generally good, with high correlation between the Jadad and VTE-specific quality scores. Short-term anticoagulation was median 1.75 months, and long-term anticoagulation was median 6.0 months. The at-risk period from B to D was median 12.8 months. Using a random-effects model, meta-analysis showed that patients who received long-term anticoagulation had fewer recurrent VTE events than did patients who received short-term anticoagulation (Table). Groups did not differ for major bleeding (Table).

CONCLUSION

In patients with venous thromboembolism, long-term anticoagulation prevents disease recurrence and does not increase major bleeding, and this clinical benefit is partially maintained after stopping treatment.

Source of funding: Not stated.

For correspondence: Dr. D. Ost, North Shore University Hospital, Manhasset, NY, USA. E-mail dost@nshs.edu.

Long-term (LT) anticoagulation (median 6.0 mo) vs short-term (ST) (median 1.7 mo) for recurrent venous thromboembolism (VTE)*

Outcomes	Number of trials	Comparisons	Weighted incidence rate (events/person-y)	Rate difference (95% CI)	Pooled incidence rate ratio (CI)
Recurrent VTE	12	LT vs ST at median 6 mo	0.02 vs 0.13	–0.11 (–0.15 to –0.07)	0.21 (0.14 to 0.31)
	11	LT vs ST at median 12.8 mo	0.05 vs 0.07	–0.02 (–0.04 to –0.00)	0.69 (0.53 to 0.91)
Major bleeding	7	LT vs ST at median 6 mo	0.01 vs 0.01	0.01 (–0.00 to 0.01)	1.80 (0.72 to 4.51)

*CI defined in Glossary.

COMMENTARY

The review by Ost and colleagues supports previous studies showing that for patients with VTE, 4 to 6 weeks of anticoagulant therapy is inferior to longer treatment and that risk for recurrent VTE during ongoing anticoagulation is negligible. In deciding on the duration of anticoagulant therapy after VTE, the most important factor seems to be the clinical setting in which VTE occurs. Thus, 3 months of anticoagulation is adequate in patients with a first episode of VTE associated with a transient risk factor (major surgery or trauma) (1), as suggested in this review. For most other patients, VTE should be considered a long-term disorder that requires treatment for at least 6 months.

In which patients, then, should treatment persist beyond 6 months? Indefinite anticoagulation is warranted in patients with active cancer (especially those with metastatic disease or who are receiving chemotherapy); multiple VTE episodes; a deficiency of antithrombin, protein C, or protein S; homozygosity for the factor V gene mutation; or persistent antiphospholipid antibodies (1). In patients with unprovoked VTE or those who are heterozygous carriers of the factor V or prothrombin gene mutations, the duration of treatment is controversial. Persistently elevated D-dimer levels or residual venous thrombosis (RVT) on ultrasonography may identify patients at high risk for recurrent VTE in whom treatment for > 6 months is warranted (2). The absence of RVT or normal D-dimer levels may identify patients at low risk for recurrence, in whom anticoagulants can be safely withdrawn (3, 4). Other patient factors, such as comorbid conditions, sex, and type of VTE presentation (deep venous thrombosis or pulmonary embolism) also may influence the duration of treatment. Additional studies are needed to identify high-risk and low-risk patient groups with unprovoked VTE in whom anticoagulant therapy can, respectively, be continued or safely withheld.

Daniel M. Witt, PharmD
Kaiser Permanente Colorado
Aurora, Colorado, USA

Sergio Siragusa, MD
University of Palermo
Palermo, Italy

References

1. **Büller HR, Agnelli G, Hull RD, et al.** Chest. 2004;126:401S-28S.
2. **Palareti G, Cosmi B.** Curr Opin Hematol. 2004;11:192-7.
3. **Siragusa S, Malato A, Anastasio R, et al.** J Thromb Haemost. 2005;3 (Suppl 1): OR176.
4. **Palareti G, Tosetto A, Cosmi B, et al.** Thromb Haemost. 2005;3(Suppl 1): H02.