6 or 3 months of anticoagulant therapy did not differ for treatment failure in patients with DVT, PE, or both

Campbell IA, Bentley DP, Prescott RJ, et al. **Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial.** BMJ. 2007;334:674.

Clinical impact ratings: Hematol/Thrombo ★★★★★★☆

QUESTION

In patients with deep venous thrombosis (DVT), pulmonary embolism (PE), or both, what is the optimum duration of oral anticoagulant therapy?

METHODS

Design: Randomized controlled trial (RCT).
Allocation: {Concealed}†.*
Blinding: {Unblinded}†.*
Follow-up period : 1 year.
Setting: 46 hospitals in the United Kingdom.
Patients: 810 patients ≥ 18 years of age (mean age 59 y, 53% men, based on 749 patients) with DVT, PE, or both, who were to receive anticoagulant therapy. Exclusion criteria included DVT or PE in the past 3 years; severe DVT or PE requiring embolectomy or thrombolysis; neoplasia in the past 3 years; polycythemia, thrombocythemia, homozygous factor V Leiden, lupus anticoagulant, or deficiency of protein C, protein S, or antithrombin; advanced multiple sclerosis, orthopedic problems of the lower limbs, or prolonged or continuous immobility for other reasons; allergy to heparin or warfarin; or need for long-term {i.e., permanent}† anticoagulant therapy.
Intervention: 6 (n = 414) or 3 months (n = 396) of anticoagulant therapy (heparin for 5 d followed by warfarin).
Outcomes: Death from DVT or PE, treatment failure (composite endpoint of nonfatal extension, failure to resolve, or recurrence during treatment), recurrence after treatment, and major bleeding. The study planned to include 2400 patients to have 80% power to detect a difference in anticipated recurrence rates of 6% and 9% in the 3-month and 6-month groups, respectively.
Patient follow-up: 91%.

MAIN RESULTS

At 1 year, groups did not differ for death from DVT or PE, treatment failure, or recurrence after treatment (Table). The 6-month group had a higher incidence of major bleeding than did the 3-month group (2.1% vs 0%, 95% CI 0.7 to 3.5).

CONCLUSION

6 or 3 months of anticoagulant therapy did not differ for treatment failure in patients with deep venous thrombosis, pulmonary embolism, or both.

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*See Glossary.
†Information provided by author.

6 vs 3 months of anticoagulant therapy (AT) for deep venous thrombosis (DVT) or pulmonary embolism (PE) at 1 year‡

Outcomes	6-mo AT	3-mo AT	RRI (95% CI)	NNH
Death from DVT or PE	0.8%	0.5%	46% (–71 to 626)	Not significant
Treatment failure§	2.6% (10/380)	1.6% (6/369)	62% (–38 to 325)	Not significant
			RRR (CI)	NNT
Nonfatal recurrence after treatment	4.2%	6.2%	32% (–24 to 63)	Not significant

‡Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.
§Composite endpoint of nonfatal extension, failure to resolve, or recurrence of DVT or PE during treatment.

COMMENTARY

Anticoagulant therapy with vitamin K antagonists is highly effective for preventing recurrent venous thromboembolism (VTE) but is associated with increased risk for bleeding. After stopping anticoagulant therapy, about 10% of patients have recurrent VTE. The optimal duration of oral anticoagulant therapy (i.e., length of treatment that minimizes risks for both recurrence and bleeding) is unclear.

The RCT by Campbell and colleagues compared 3 and 6 months of anticoagulant therapy in patients with VTE, most of whom had idiopathic VTE without antecedent risk factors. At face value, this study suggests similar efficacy with 3 and 6 months of anticoagulant therapy, as both durations were associated with similar risks for treatment failure during treatment and recurrent VTE after treatment was stopped. However, several drawbacks may preclude this conclusion. First, only 749 patients were included (instead of the planned sample size of 2400); this sample may have been too small to detect the prespecified 3% difference in rates of recurrent VTE. Second, the clinical significance of treatment failure, specifically extension of the clot or failure to resolve, is controversial. Although the risk for recurrent VTE did not differ in the 3- and 6-month groups (relative risk increase 1.5%, CI 0.8 to 2.9), a modest but potentially important benefit with 6 months of anticoagulant therapy cannot be excluded. We do not know what the results might have been with a larger group or longer follow-up. Finally, results were not analyzed separately for patients with idiopathic or secondary VTE, although most patients appeared to have idiopathic VTE.

This important study adds to the knowledge that patients with a first VTE should receive anticoagulant therapy for ≥ 3 months. Clinical practice guidelines distinguish treatment duration in patients with VTE associated with transient risk factors (3 to 6 mo) or idiopathic VTE (6 to 12 mo) because of the higher risk for recurrent VTE in the latter group. Although this recommendation is not overruled by this study, the lower bleeding risk and good risk–benefit ratio suggest that 3 months of anticoagulant therapy might be used in selected patients with idiopathic VTE, such as those at higher risk for bleeding. Ultimately, what is needed to tailor treatment duration is identification of individual risk factors that stratify patients according to risk for recurrent VTE.

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