⮞ **MILESTONE 11**

Quest to find the optimal duration

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Venous thromboembolism — a disease process involving the formation of blood clots that manifests as deep-vein thrombosis or pulmonary embolism — is typically treated with anticoagulant therapy. This practice was first begun in 1969 by William Coon, Park Willis, and Michael Symons, who reported that the frequency of recurrent thromboembolism in the first 12 weeks after discharge could be reduced with several months of heparin treatment. However, given the retrospective nature of the study, firm conclusions regarding the effectiveness of heparin in this context could not be drawn. A decade later, results from a randomized, controlled trial by Hull and colleagues confirmed the benefit of anticoagulant therapy in preventing recurrent venous thromboembolism, in addition to showing that warfarin therapy was more effective than subcutaneous heparin in this setting (MILESTONE 5). As predicted, this increased effectiveness was associated with an elevated risk of bleeding.

Subsequent trials sought to compare the benefits and risks of different lengths of vitamin K antagonist treatment for venous thromboembolism in an attempt to identify the shortest duration of anticoagulation that reduces the risk of recurrence to its lowest level. Results from several small, randomized studies published in the 1970s and 1980s suggested that shortening the duration of anticoagulation from 3 or 6 months to 3–6 weeks does not result in an increase in the risk of recurrence. However, in 1995, investigators in the multicentre, randomized DURAC trial reported a significant reduction in the risk of recurrent thromboembolism upon extension of oral anticoagulant therapy from 6 weeks to 6 months. This study was the first reliably to demonstrate a benefit of prolonged anticoagulation across several patient subgroups, and the risk of major haemorrhage remained low even in the 6-month treatment group.

The question thus remains: what is the optimal length of vitamin K antagonist treatment for venous thromboembolism? Two major limitations of the numerous subsequent studies that have attempted, but largely failed, to answer this question are their capacity to compare only two durations of treatment, and their small numbers of patient. To address these limitations, in 2011, investigators in seven studies that compared different durations of vitamin K antagonist treatment for venous thromboembolism pooled individual patient data from their studies, with the goal of identifying the shortest length of treatment that is associated with the lowest risk of recurrence. This study design increased both the spectrum of treatment durations evaluated and the number of patients studied. In addition, patients could be categorized into subgroups according to the location of the initial venous thromboembolism, and whether the thrombosis was provoked by a temporary risk factor, because these variables might influence risk of recurrence.

A total of 2,925 participants were included in the pooled study, corresponding to 4,023 patient-years of follow-up. The duration of anticoagulant treatment was 12 or 27 months in 12% of patients, 6 months in 27%, 3 months in 36%, and 1.0 or 1.5 months in 25%. The risk of recurrent venous thromboembolism in the 24-month period after cessation of anticoagulation therapy varied between the four treatment groups. Risk of recurrent venous thromboembolism was highest in the patients treated for 1.0 or 1.5 months, but similar between patients treated for 3 months, 6 months, and 12 or 27 months.

"[I]f patients with venous thromboembolism do not have an indication for indefinite anticoagulant treatment they generally should stop treatment at 3 months," concluded the investigators. Importantly, the initial presentation of venous thromboembolism seems to be important, because the risk of recurrence after stopping anticoagulation treatment doubled in patients with pulmonary embolism or proximal deep-vein thrombosis compared with those with an isolated distal deep-vein thrombosis. Although extending treatment from 3 months to 6 months in these patients might reduce the risk of recurrence, this benefit must be balanced against a higher risk of bleeding and increased costs associated with prolonged treatment.

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FURTHER READING Makaryus, J. N. *et al.* Oral anticoagulants in the management of venous thromboembolism. *Nat. Rev. Cardiol.* **10**, 397–409 (2013)