MILESTONE 5

High-dose heparin for secondary prevention

By the end of the 1970s, two anti-coagulant therapies were available for the treatment of thromboembolic disorders: oral anticoagulant therapy with vitamin K antagonists (MILESTONE 3) and intravenous injection of heparin (MILESTONE 4). Patients with venous thromboembolism were initially treated with intravenous administration of unfractionated heparin for ≥ 5 days. The standard practice was to follow this initial treatment by long-term oral anticoagulant therapy, most commonly with warfarin, to prevent the recurrence of venous thromboembolism. However, the strategy of using oral anticoagulants for secondary prevention was based on a retrospective study with no randomization. Moreover, vitamin K antagonists are associated with a high risk of bleeding complications. These issues prompted Russell Hull and colleagues to assess in a randomized way the use of oral anticoagulants for the secondary prevention of recurrent venous thromboembolism, and to compare this therapy with low-dose subcutaneous heparin, which had been shown to be associated with a lower risk of bleeding.

In a study published in 1979, Hull *et al.* assigned a total of 68 patients with deep-vein thrombosis to initial treatment with intravenous heparin and then randomly allocated the patients to secondary prevention with either low-dose, subcutaneous heparin (5,000 units every 12 h) or warfarin in doses adjusted according to the prothrombin time (maintained at 1.5–2.0 times the control value with weekly monitoring). The trial showed that therapy with adjusted-dose warfarin was more effective for the prevention of recurrent venous thromboembolism than therapy with low-dose subcutaneous heparin: none of the 33 patients receiving warfarin had a new episode of venous thromboembolism; by contrast, nine of the 35 patients receiving low-dose heparin had recurrent venous

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thromboembolism ($P=0.001$). However, use of warfarin was associated with a higher risk of bleeding than therapy with low-dose subcutaneous heparin: seven patients in the warfarin group had haemorrhagic complications compared with none in the group receiving low-dose heparin ($P<0.005$). Of note, a new episode of venous thromboembolism occurred only in those patients who had proximal-vein thrombosis at baseline.

Given that low-dose subcutaneous heparin, although safer than warfarin, was ineffective for the prevention of venous thrombosis, Hull and colleagues initiated a new randomized clinical trial to assess the efficacy and safety of higher doses of subcutaneous heparin. For this study, 106 patients with acute proximal-vein thrombosis were treated first with intravenous heparin and then randomly assigned to secondary prophylaxis with either adjusted-dose subcutaneous heparin or warfarin in a dose adjusted to 1.5–2.0 times the control value with weekly monitoring. The subcutaneous heparin dose was adjusted at the start of the study and afterwards was fixed (to a mean dose of 10,000 units every 12 h), with the aim of assessing a therapy that did not require continuous monitoring,

“low-dose subcutaneous heparin, although safer than warfarin, was ineffective for the prevention of venous thrombosis”

which would be more convenient for the long-term treatment required for secondary prevention.

Adjusted-dose subcutaneous heparin was as effective as warfarin, with an incidence of recurrent venous thromboembolism of 1.9% among patients receiving warfarin and 3.8% in patients receiving subcutaneous heparin. However, as in the previous trial, use of subcutaneous heparin was safer than the use of warfarin (17.0% of the patients in the warfarin group had bleeding complications compared with 1.8% in the heparin group).

This trial demonstrated that high-dose, subcutaneous heparin is an effective alternative to the use of warfarin for secondary prophylaxis in patients with venous thromboembolism. Both heparin and vitamin K antagonists remained the standard treatment for venous thromboembolism until the development of more convenient and safer alternative anticoagulants (MILESTONES 7–10).

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ORIGINAL ARTICLES Hull, R. *et al.* Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N. Engl. J. Med.* **301**, 855–858 (1979) | Hull, R. *et al.* Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. *N. Engl. J. Med.* **306**, 189–194 (1982)

FURTHER READING Wolberg, A. S. *et al.* Venous thrombosis. *Nat. Rev. Dis. Primers* **1**, 15006 (2015)