MILESTONE 7

A breakthrough for out-of-hospital treatment of thrombosis

Since the discovery of heparin in 1916 (MILESTONE 1) and vitamin K antagonists in 1940 (MILESTONE 2), these agents have become the standard anticoagulation therapy to prevent or treat thromboembolic disorders. However, both of these anticoagulant agents have many drawbacks, including an unpredictable anticoagulant response, which requires frequent laboratory monitoring of coagulation activity to adjust the dose. The development of low-molecular-weight heparins (LMWHs) in the late 1970s and early 1980s opened the way to new indications for the prevention and treatment of venous thromboembolism.

LMWHs are prepared by depolymerization of heparin (which has a molecular mass of 12,000–16,000 Da) to yield fragments of 4,000–5,000 Da. Like unfractionated heparin, the major anticoagulation effect of LMWHs is mediated by activation of antithrombin, the main inhibitor of coagulation enzymes. Unlike unfractionated heparin, binding of LMWHs promotes the inactivation mainly of factor Xa and, to a lesser extent, thrombin because most LMWHs are too short to catalyse thrombin inhibition, but can induce the inhibition of factor Xa.

> “Elimination of intravenous injection and laboratory monitoring suggested that LMWHs could allow patients to be treated at home”

Science Photo Library / Alamy Stock Photo

Initial studies showed that LMWHs were at least as effective and safe as unfractionated heparin for the treatment of deep-vein thrombosis, and more convenient to use. The lower levels of unspecific binding of LMWHs to plasma proteins and cells compared with unfractionated heparin — which led to a longer plasma half-life, better bioavailability, and a more predictable anticoagulant response — allowed LMWHs to be administered subcutaneously instead of intravenously and in a fixed or weight-adjusted dose without the need for routine laboratory monitoring.

The elimination of intravenous injection and laboratory monitoring suggested that LMWHs could allow patients to be treated at home for thrombotic diseases such as deep-vein thrombosis or pulmonary embolism, which at the time required hospitalization for initial therapy with intravenous unfractionated heparin followed by oral anticoagulant therapy (most commonly with warfarin) for ≥3 months. An alternative, at-home treatment would be more convenient for patients, lower the risk of nosocomial infection, and reduce the cost to health-care systems.

The demonstration that unmonitored, out-of-hospital, subcutaneous administration of LMWHs was as effective and safe as in-hospital, intravenous administration of unfractionated heparin for the treatment of thromboembolic disorders came in 1996 and 1997 with the publication of four large randomized clinical trials. In 1996, Levine *et al.* and Koopman *et al.* showed that the rates of recurrent thromboembolism and major bleeding in patients with deep-vein thrombosis were similar with the use of either LMWH or unfractionated heparin; however, treatment with LMWH allowed most of the patients to be treated at home or to be discharged early from the hospital. These initial trials included only patients with asymptomatic venous thrombosis. The efficacy and safety of unmonitored, subcutaneous administration of LMWH for the treatment of symptomatic thrombosis was confirmed in 1997 in the COLUMBUS study, which included symptomatic patients with venous thrombosis or pulmonary embolism, and the study by Simonneau *et al.*, which included patients with symptomatic pulmonary embolism.

The findings from these trials changed the approach to the management of thrombosis, and LMWH progressively replaced unfractionated heparin for the prevention and initial treatment of thrombotic diseases. Nevertheless, the many drawbacks of LMWHs — including the administration by injection, the need for close monitoring in patients at extremes of weight, and the contraindication in patients with kidney disease because LMWHs are cleared mostly by the renal route— meant that the search to find safer and more convenient anticoagulants was still ongoing.

Irene Fernández-Ruiz,
Senior Editor, *Nature Reviews Cardiology*

ORIGINAL ARTICLES Levine, M. *et al.* A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N. Engl. J. Med.* **334**, 677–681 (1996) | Koopman, M. M. *et al.* Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N. Engl. J. Med.* **334**, 682–687 (1996) | The COLUMBUS Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N. Engl. J. Med.* **337**, 657–662 (1997) | Simonneau, G. *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N. Engl. J. Med.* **337**, 663–669 (1997)
FURTHER READING Hirsh, J. A review of the results of recent studies of the treatment of venous thromboembolism and unstable angina. *Circulation* **98**, 1575–1582 (1998)