Treatment of Venous Thromboembolism with Low-Molecular-Weight Heparin

Russell D. Hull and Graham F. Pineo
Head, Division of General Internal Medicine, Foothills Hospital, Calgary, Alberta T2N2T9 Canada

Summary. There is now ample evidence to indicate that certain low-molecular-weight heparins given subcutaneously can replace continuous intravenous unfractionated heparin for the initial treatment of venous thromboembolism. The low-molecular-weight heparins have a predictably high absorption rate when given subcutaneously and a prolonged duration of action, permitting them to be given by a once or twice daily injection for the prevention or treatment of venous thrombosis. Furthermore, treatment does not require laboratory monitoring, thus eliminating the need for continuous IV infusion and permitting the early discharge of patients with venous thromboembolism. This should eventually lead to the outpatient treatment of venous thromboembolism. Studies to date indicate that low-molecular-weight heparin is more cost-effective than unfractionated heparin in the treatment of venous thromboembolism and the cost effectiveness will be increased by out-of-hospital treatment. At the present time, the findings associated with any individual low-molecular-weight heparin preparation cannot be extrapolated to different low-molecular-weight heparins, and therefore each must be evaluated in separate clinical trials. The information to date is that low-molecular-weight heparin is safer and more effective than continuous intravenous unfractionated heparin in the treatment of proximal venous thrombosis. The decreased mortality rate seen in two clinical trials, particularly in patients with metastatic cancer, was quite unexpected. This requires further confirmation in larger prospective randomized trials.

Key Words. low molecular weight heparin, venous thromboembolism, venous thrombosis

The accepted initial treatment of acute venous thromboembolism is continuous intravenous heparin for 5–6 days [1–3] with warfarin starting on day 1 or 2 [4,5] and continued for 3 months. The therapeutic range for heparin is an APTT value of 1.5–2.5 times the mean of the control to provide a heparin blood level of 0.2–0.4 units/ml using protamine sulphate inhibition. The targeted INR for warfarin is 2.0–3.0. With improvements in clinical trials methodology and the use of accurate objective tests to detect venous thromboembolism, it has been possible to perform a series of randomized clinical trials to evaluate various methods of treatment of venous thromboembolism. Thus, the therapeutic ranges for intravenous heparin and oral warfarin have been shown to be effective in decreasing the recurrence rate of venous thromboembolism as well as providing an acceptably low incidence of major bleeding. Patients who fail to achieve a therapeutic APTT (>1.5 × control) within the initial 24 hours or more have a much greater tendency to develop recurrent venous thromboembolism during the 3 month period as compared with those who are therapeutic [3,8,9]. Most of the symptomatic recurrences occurred after the first month of treatment. The use of less intense warfarin (INR 2.0–3.0) was shown to be as effective as higher intensity warfarin (INR 3.0–4.5) with a markedly reduced incidence of major bleeding [7]. Bleeding in patients on warfarin can be directly related to elevation of the INR above the therapeutic range [7], but there is little evidence that bleeding on heparin is associated with APTT above the therapeutic range (>2.5 × control) [6]. Bleeding on heparin, however, can be directly related to the underlying clinical risk for bleeding, such as recent surgery, peptic ulcer disease, or recent stroke [6].

Unless a heparin protocol is used, many patients will remain subtherapeutic for extended periods of time and thus be placed at significant risk of recurrent venous thromboembolism and death [10,11]. A heparin protocol will ensure that virtually all patients (98–99%) will achieve the therapeutic range of APTT within the initial 24 hours of treatment and thereby decrease the likelihood of recurrent thromboembolism with no added risk of bleeding [6,9].

In the past a number of randomized clinical trials have compared the effectiveness and safety of heparin given by twice-daily subcutaneous injection with continued intravenous heparin. It was concluded in a meta-analysis that subcutaneous heparin was at least as effective and safe as intravenous heparin [12]. In view of the well-established need to achieve a lower limit of the therapeutic range by APTT or heparin level measurements [6,9,13] and the demonstration that subcutaneous heparin frequently resulted in subtherapeutic therapy as measured by APTT or heparin levels, subcutaneous heparin cannot be recom-
mended in the initial treatment of proximal venous thrombosis. Furthermore, there is growing evidence that the initial use of inadequate heparin may lead to the need for markedly increased heparin doses over the subsequent 5 or 6 days. Such heparin resistance was most evident in patients who subsequently developed recurrent venous thromboembolism [14].

For all of these reasons, the possible role of low-molecular-weight heparin in the initial treatment of venous thromboembolism has been anticipated with great interest. In recent years, a number of low-molecular-weight heparin derivatives of commercial heparin have been prepared by a variety of techniques. The mean molecular weight of the low-molecular-weight heparins is in the range of 4000–5000 Da, compared with 12,000–16,000 Da for unfractionated heparin [15]. Pharmacokinetic studies [16–21] and recent small clinical trials in selected patients with venous thrombosis [22–26] indicated that the availability of the low-molecular-weight heparin fractions following subcutaneous injection was very high.

Studies in healthy volunteers [18] reported that the bioavailability of low-molecular-weight heparin after a single subcutaneous injection of 120 factor X a units/kg was approximately 90% of an equivalent intravenous dose. This excellent bioavailability of low-molecular-weight heparin, along with the longer half-life of the anticoagulant activity as measured by anti-factor X a activity (as compared with unfractionated heparin) [16–19,21,27], suggested that it may be possible to develop an effective regimen for the initial treatment of venous thromboembolism using a once-daily subcutaneous injection of low-molecular-weight heparin. Furthermore, the anticoagulant response as measured by factor X a inhibitor units/ml observed with a given dose of low-molecular-weight heparin was highly correlated with body weight [21]. This suggested that low-molecular-weight heparin could be given by a fixed dose (in terms of factor X a units/kg) without any laboratory monitoring.

Studies in experimental animal models of venous thrombosis has shown that some low-molecular-weight heparin fractions have equal (or greater) antithrombotic efficacy, but with less hemorrhagic effects when compared with unfractionated heparin [15,28–31]. Two recent meta-analyses have compared the efficacy and safety of low-molecular-weight heparin with unfractionated heparin [32,33]. Both studies indicated that low-molecular-weight heparin was more effective than unfractionated heparin in the prevention of postoperative deep vein thrombosis. However, both studies revealed that bleeding complications were somewhat higher with the use of low-molecular-weight heparin as compared with unfractionated heparin, particularly when some of the studies in general surgery, which had weaker methodology, were excluded.

Similarly, in a recent large multicenter trial comparing the use of low-molecular-weight heparin (Logiparin) with oral warfarin in the prevention of venous thrombosis following total joint replacement, low-molecular-weight heparin was shown to be more effective than warfarin in preventing deep vein thrombosis, but with a higher incidence of bleeding [34]. On the other hand, a large clinical trial in patients undergoing general surgery indicated that low-molecular-weight heparin (Fragmin) was as effective as unfractionated heparin in preventing postoperative venous thrombosis and was associated with a lower incidence of serious bleeding [35]. This may reflect the fact that higher doses of low-molecular-weight heparin are used in high risk situations, for example, total hip replacement as compared with those used in general surgery.

In many European countries, low-molecular-weight heparin has replaced unfractionated heparin for the prevention of venous thrombosis because of its improved efficacy and the convenience of once-daily administration without the need for monitoring [36]. One such agent is available in North America for a twice-daily subcutaneous injection for the prevention of venous thrombosis following major orthopedic surgery, and two have been approved for thromboprophylaxis following general surgery. Others are currently under review for treatment indications, but none as yet has been approved.

### Randomized Clinical Trials Evaluating the Use of Low-Molecular-Weight Heparin for the Treatment of Proximal Venous Thrombosis

A number of randomized clinical trials have compared low-molecular-weight heparin with unfractionated heparin for the initial treatment of patients with proximal venous thrombosis. In a number of these studies, continuous intravenous low-molecular-weight heparin was compared with continuous intravenous unfractionated heparin [37–39,43]. Two trials compared subcutaneous low-molecular-weight heparin with subcutaneous unfractionated heparin [26,49], and three studies compared subcutaneous low-molecular-weight heparin with continuous intravenous unfractionated heparin [46–48]. The findings of the various clinical trials are summarized later.

In an exploratory study evaluating the effectiveness of low-molecular-weight heparin in the treatment of venous thrombosis, patients with venographically proven deep vein thrombosis (DVT) were randomized to treatment with a continuous intravenous infusion of either low-molecular-weight heparin or unfractionated heparin [39]. The initial dose was 240 units (anti–X a)/kg/12 hr. This initial study was stopped after entering 27 patients because two postoperative patients