MILESTONE 4

Low-dose heparin for VTE — prevention is better than cure

Heparin entered clinical testing in the 1930s and, in combination with a vitamin K antagonist, was shown in the 1950s to be effective in the treatment of acute pulmonary embolism (MILESTONE 3). Pulmonary embolism is a common complication in patients undergoing abdominal, thoracic, or urological surgery, and can kill a patients within 30 min of the embolic event, meaning that the window for diagnosing and treating the condition is very limited. Accordingly, in the 1970s, clinicians undertook a series of clinical trials to assess the prophylactic use of low-dose heparin to prevent postoperative venous thromboembolism (VTE).

In the mid-1970s, a total of 27 clinical trials into this topic were published. The largest of these was an international, multicentre, randomized trial published in *The Lancet* in 1975. A total of 4,121 patients undergoing a variety of elective major surgical procedures were randomly assigned to receive low-dose heparin ($n = 2{,}076$) or control ($n = 2{,}045$). Overall, 80 patients died in the heparin group, and 100 patients died in the control group; of these patients, 66% and 72% in each group, respectively, underwent post-mortem examination. Only two patients in the heparin group compared with 16 patients in the control group were found to have died from acute massive pulmonary embolism ($P < 0.005$).

A subset of patients (625 in the heparin group and 667 in the control group) underwent ^{125}I-fibrinogen testing to detect deep-vein thrombosis (DVT). The frequency of DVT was significantly lower in the heparin group than in the control group (7.7% versus 24.6%; $P < 0.005$). In 30 patients, DVT was detected at post-mortem: six in the heparin group and 24 in the control group ($P < 0.005$). No significant difference in the requirement for blood transfusion owing to operative or postoperative bleeding was found between the groups.

In 1978, Vijay V. Kakkar published a summary of the various clinical trials, which supported the findings of the 1975 trial. Together, the trials involved >4,000 patients. The mean incidence of venous thrombosis was approximately 7% in patients who received low-dose heparin compared with 25% in controls.

Although prevention of venous thrombosis is of fundamental importance, the source of most major pulmonary emboli is extending thrombi in the proximal veins of the lower limbs, so the efficacy of low-dose heparin to prevent this phenomenon was also assessed. In 1,479 patients who received heparin, thrombi were detected in 6% of patients, and thrombus extension occurred in only 0.6%. By contrast, in 1,631 patients in the control group, thrombi were detected in 23% of patients, and extension of the thrombus occurred in 6%.

Low-dose heparin "is highly effective in preventing postoperative fatal pulmonary embolism" and "does not produce serious bleeding", concluded Kakkar. The standard dosage regimen was 5,000 units of heparin given 2 h before surgery and then every 8–12 h for 7 days thereafter or until the patient was fully mobile, whichever was the longer period. "This form of prophylaxis can now be recommended for use on a large scale in high-risk patients undergoing major abdominal, thoracic, and urological operations, as well as in medical patients at moderate risk of developing thromboembolic complications." The wide adoption of this an approach was predicted to save thousands of lives per year. Subsequent studies focused on the use of low-dose versus full-dose heparin for the treatment and secondary prevention of VTE (MILESTONE 5).

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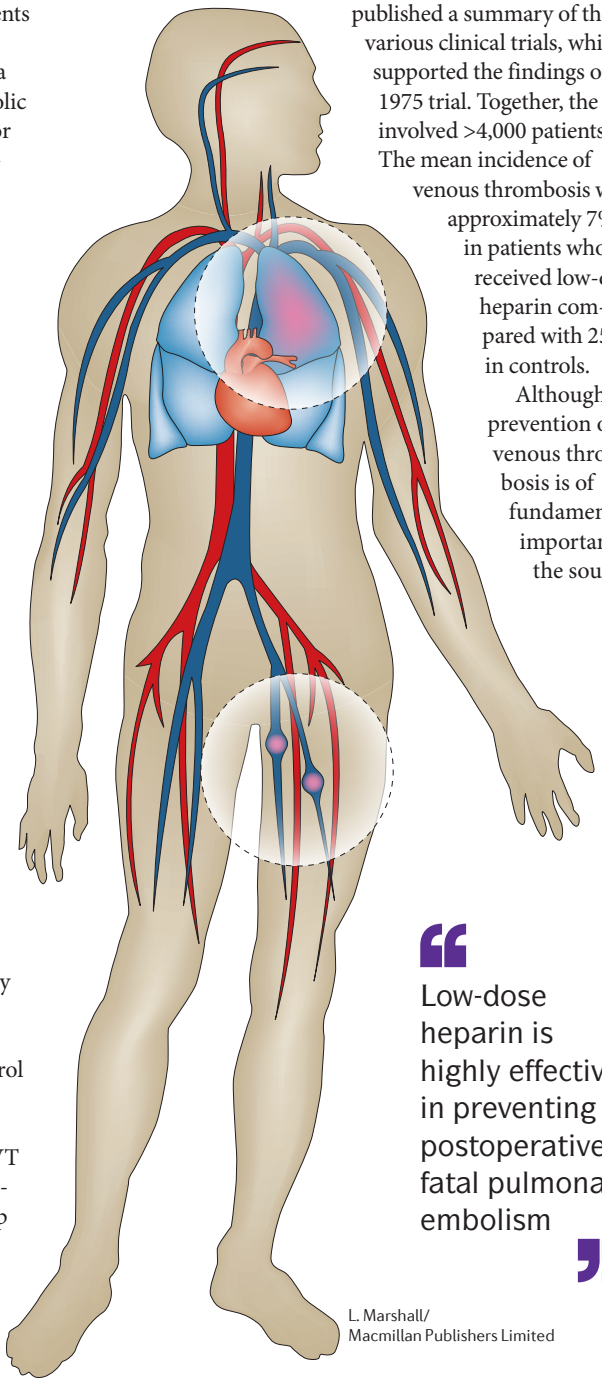

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> "Low-dose heparin is highly effective in preventing postoperative fatal pulmonary embolism"

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