How we changed our approach to venous thromboembolism

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TITLE	Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis.
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Thirty years ago, *The Lancet* published the results of a randomized clinical trial comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) for the treatment of proximal deep vein thrombosis (DVT).[1] The study was carried out at a single Italian center and enrolled a total of 170 patients over 5 years (from 1986 to 1991).

At that time, the standard treatment for DVT and pulmonary embolism (PE) consisted of UFH, administered by a continuous intravenous infusion for approximately 10 days, followed by vitamin K antagonists. This treatment relied on laboratory measurements of the activated partial thromboplastin time (aPTT) and prothrombin time/International Normalized Ratio and on consequent dose adjustments. Not uncommonly, patients were hospitalized (and confined to bed) for 2 weeks or more.

In the 1980s, LMWH were developed and proposed as an alternative to UFH for the prevention and treatment of thromboembolic disorders. LMWH offered, for the first time, the possibility of administering an anticoagulant drug at fixed doses, without the need for laboratory monitoring. However, the first studies comparing LMWH with UFH in the treatment of venous thrombosis still used the laboratory to determine the correct dose of LMWH and all studies published before the Italian trial used surrogate markers to assess therapeutic efficacy.

It was about time to test LMWH without laboratory support and to assess the occurrence of symptomatic events, recurrence or extension of DVT and bleeding, to reflect clinical practice. Needless to say, the idea of administering an anticoagulant drug to a patient with an extensive thrombosis and at potential risk of fatal PE without any information on treatment intensity from the laboratory was not as easy to accept as we may find it now.

In the study published in *The Lancet*, 85 patients received intravenous UFH with a target aPTT of 1.5 to 2.0 times the pretreatment value and 85 patients received twice daily fixed, weight-adjusted doses of the LMWH nadroparin. Warfarin was started after 7 days of heparin treatment and heparins were discontinued on day 10, or later if the INR was still below 2.0. After a 6-month follow-up, 12 recurrent thrombotic events had occurred in the group treated with UFH and six in the LMWH group; four and one of these events, respectively, were diagnosed during parenteral treatment. As shown in Figure 1, three recurrent events in each group were fatal PE, but only one (in a patient on LMWH) occurred during parenteral treatment. Bleeding events defined as severe occurred in three patients receiving UFH (all retroperitoneal bleeds) and in one patient receiving LMWH (hematemesis). The study was not sufficiently powered to show statistically significant differences between groups, but LMWH clearly appeared to be at least as effective and safe as UFH and the authors hypothesized future changes in the management of venous thrombosis. These changes included the possibility of allowing patients to be fully ambulant thanks to the subcutaneous administration of LMWH and the possibility of outpatient management thanks to the fact that laboratory monitoring was not needed.

These hypotheses were confirmed a few years later by two randomized studies that demonstrated that subcutaneous LMWH administered out of hospital without laboratory monitoring is as effective and safe as continuous infusion of UFH given in hospital.[2,3] Following the results of these studies, in a few years the management of venous thrombosis changed dramatically, with more than 90% of patients with DVT and selected patients with low-risk PE being treated out of hospital. These changes clearly improved the quality of life of patients with venous thrombosis and resulted in lower costs of management.

More than 10 years later, LMWH also became the standard treatment for cancer-associated venous thrombosis, as a single-drug approach, and more than 20 years later direct oral anticoagulants are further contributing to simplify the management of venous thrombosis.

Disclosures

No conflicts of interest to disclose.

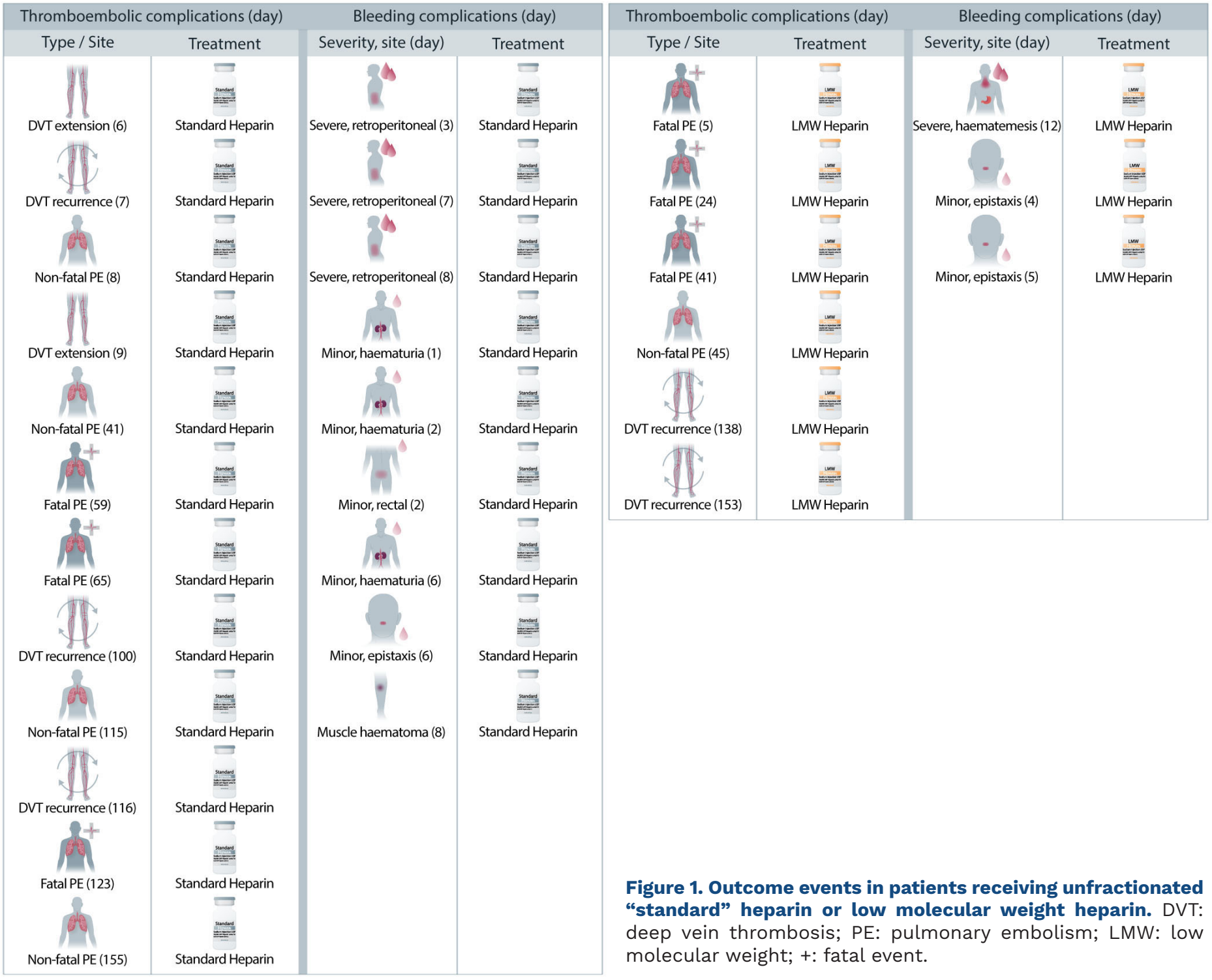

Figure 1. Outcome events in patients receiving unfractionated "standard" heparin or low molecular weight heparin. DVT: deep vein thrombosis; PE: pulmonary embolism; LMW: low molecular weight; +: fatal event.

References

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