

## The Use of Low-Molecular-Weight Heparins in Acute Coronary Syndromes

We thank Jennifer Spencer for her well-written summary of the use of low-molecular-weight heparins in acute coronary syndromes.<sup>1</sup> However, the statement that “only enoxaparin has shown superior efficacy over unfractionated heparin and would be considered the low-molecular-weight heparin of choice” seems to be a popular opinion supported by shrewd marketing practices, not by adequate evidence. We have reservations regarding the results of the enoxaparin trials and are not convinced that it is superior to other low-molecular-weight heparins in acute coronary syndromes. We offer the following evidence to support our position.

In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial,<sup>2</sup> anticoagulation with unfractionated heparin was suboptimal, and this may have biased the results in favour of enoxaparin.<sup>3</sup> First, the target range of activated partial thromboplastin time was determined by a ratio method, which has been shown *not* to be an accurate means of determining the target range (T. Trujillo, PharmD, Beth Israel Deaconess Medical Center and Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Massachusetts, personal communication, December 2, 1998). Second, an empirical dosage protocol resulted in fewer than half of the patients treated with unfractionated heparin achieving an activated partial thromboplastin time within the target range by 24 h. In fact, 14.8% to 18.0% of the activated partial thromboplastin times were subtherapeutic for the duration of heparin therapy.<sup>2</sup> Third, the median duration of therapy was only 2.6 days. It has been shown that an average of 5 to 6 days of treatment with unfractionated heparin plus acetylsalicylic acid results in a lower frequency of death or acute myocardial infarction than treatment with acetylsalicylic acid alone, whereas no such difference is seen when the duration of treatment with unfractionated heparin is reduced to 2 days.<sup>4</sup>

The data from the Thrombolysis in Myocardial Infarction (TIMI) 11B study<sup>5</sup> should be interpreted with caution. The primary outcome at day 8 was not a direct comparison of unfractionated heparin with low-molecular-weight heparin but rather a comparison of 8 days of enoxaparin therapy with 3 days of treatment with unfractionated heparin.<sup>6</sup> By contrast, in the trials involving dalteparin (Fragmin in Unstable Coronary Artery Disease Study [FRIC]<sup>7</sup>) and nadroparin (FRAXiparine in Ischaemic Syndrome [FRAX.I.S.]<sup>8</sup>), the treatment duration for these agents was similar to that of unfractionated heparin (6 days).

The use of less-well-defined outcomes, such as recurrent angina or need for revascularization, is questionable. At no time during the ESSENCE<sup>2</sup> and TIMI

11B<sup>5</sup> trials was there a statistically significant difference in rate of death or myocardial infarction. In fact, we believe that the ESSENCE trial<sup>2</sup> provides solid evidence that there is no difference between enoxaparin and unfractionated heparin with respect to the individual end points of death, myocardial infarction, and major bleeding. Statistical significance was attained only by adding recurrent angina to create a composite end point.

Finally, a recent meta-analysis<sup>6</sup> that examined the end points of death, myocardial infarction, and bleeding for all the clinical trials of low-molecular-weight heparin in acute coronary syndrome reported to date found no difference between any of the low-molecular-weight heparins and unfractionated heparin. The authors concluded that “the totality of the evidence does not support the concept that [low-molecular-weight heparin] is superior. Therefore, it is inappropriate to emphasize selected trial results and claim that ESSENCE and TIMI 11B provide clear evidence of superiority of enoxaparin over [unfractionated heparin]”.

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### References

1. Spencer J. The use of low-molecular-weight heparins in acute coronary syndromes. *Can J Hosp Pharm* 2000;53:104-12.
2. Cohen M, Demers C, Gurfinkel EP, Turpie AGG, Fromwell GJ, Goodman S, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447-52.
3. Trujillo TC, Nolan PE Jr. Unfractionated heparin in acute coronary syndromes: Has its time come and gone? *Am J Health Syst Pharm* 1998;55:2402-9.
4. Turpie AG. Can we differentiate the low-molecular-weight heparins? *Clin Cardiol* 2000;23(Suppl 1):14-7.
5. Antman EM, McCabe CH, Gurfinkel EP, Turpie AGG, Bernink PJLM, Salein D, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
6. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936-42.
7. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AGG, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. *Circulation* 1997;96:61-8.
8. The FRAX.I.S. Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;20:1553-62.



## Reply and Corrections:

I would like to thank Mr Filiatrault and Mr Zaremba for their letter, which highlights many of the issues in the controversy surrounding the trials of low-molecular-weight heparins in acute coronary syndromes. The recently published meta-analysis by Eikelboom and others<sup>1</sup> provides an excellent discussion of this topic and a detailed analysis of the individual issues. Eikelboom and others<sup>1</sup> point out that the available evidence does not definitively favour enoxaparin over unfractionated heparin. Such evidence could be obtained only through a trial comparing the various low-molecular-weight heparins with unfractionated heparin in the same research setting, but a trial of this kind is unlikely to be undertaken.

I would also like to take this opportunity to advise readers that the following changes are needed to my original article on low-molecular-weight heparins in the treatment of acute coronary syndromes.<sup>2</sup>

First, the anticoagulant effects of low-molecular-weight heparins can be partially reversed by protamine.<sup>3</sup> Readers should consult individual product monographs for directions on how to accomplish this intervention, should reversal be required.

Second, a correction is needed to the discussion of the FRagmin and Fast Revascularisation during InStability in Coronary artery disease trial (FRISC II).<sup>4</sup> In my article, both Table 3 and the text indicate that 1049 patients were initially given "dalteparin 120 U/kg SC bid for at least 5 days, and 1056 patients received unfractionated heparin adjusted for activated partial thromboplastin time. The patients who had received dalteparin were then randomly assigned into a double-blind extended trial to receive a fixed dose of dalteparin or placebo for 3 months, on the basis of weight and sex."

In fact, patients were initially treated with either SC dalteparin or unfractionated heparin until 72 h. They were then given dalteparin 120 U/kg SC every 12 h (maximum dose 10 000 U) for at least 5 days. Patients were then randomly assigned to receive either dalteparin SC injections (1049 patients) or placebo injections (1056 patients) twice daily for a total of 3 months. Throughout the trial, the patients received a maintenance dose of acetylsalicylic acid.<sup>4</sup>

I apologize for these erroneous statements in the published article.

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## References

1. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936-42.
2. Spencer J. The use of low-molecular-weight heparins in acute coronary syndromes. *Can J Hosp Pharm* 2000;53:104-12.
3. Ramamurthy N, Baliga N, Wakefield TW, Andrews PC, Yang VC, Meyerhoff ME. Determination of low-molecular-weight heparins and their binding to protamine and a protamine analog using polyion-sensitive membrane electrodes. *Anal Biochem* 1999;266:116-24.
4. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-7.

## Impact of Adding a Low-Molecular-Weight Heparin to the Drug Formulary of a Small Hospital

In September 1999 the low-molecular-weight heparin dalteparin was added to the formulary of the Nipawin Hospital, Nipawin, Saskatchewan, for use as an alternative to full-dose unfractionated heparin in the treatment of systemic venous thromboembolism and acute coronary syndrome. At the time, we reviewed the global economic implications of using a low-molecular-weight heparin in our 50-bed hospital and identified one cost that has not been considered in other reviews — the cost to call back laboratory personnel to monitor activated partial thromboplastin time. Our regular laboratory hours are 0730 to 1600, Monday to Friday, and 0700 to 1100 on weekends. Therefore, when initiating therapy with unfractionated heparin, it is only through great coincidence that there is not at least one call-back for staff to perform a test for activated partial thromboplastin time. The average cost in our facility for a laboratory call-back is about \$65.

For the treatment of venous thromboembolism, we felt that using a low-molecular-weight heparin would simplify administration and allow for outpatient treatment in selected patients. We estimated that our cost (including the drug, administration supplies, laboratory work, and call-back for laboratory personnel) to treat one patient with unfractionated heparin for 6 days was approximately \$96; with dalteparin the cost would rise by about \$26, to \$122.

In patients with acute coronary syndrome, we estimated an average treatment duration of 2.5 days with a heparin product. Traditionally, we have administered heparin to patients for about 24 h past their last episode of chest pain; if the chest pain does not resolve within

