Enoxaparin in unstable coronary artery disease

In the Dr Cannon's editorial, concerning the role of enoxaparin in ST elevation myocardial infarction, published in the issue of 15 April 2002[1], it is stated that in the only direct comparison of two molecular weight heparins in unstable angina and non-ST myocardial infarction, enoxaparin had a significantly lower rate of death, myocardial infarction or recurrent ischaemia than tinzaparin. This suggests that enoxaparin is in fact a superior low molecular weight heparin. This sentence is based on the EVET study, published in abstract form[2]. The primary end-points of this study were death, myocardial infarction, refractory angina and recurrence of unstable angina. The specified duration of treatments for both enoxaparin and tinzaparin was 7 days. Two aspects deserve comment: on the one hand, it is certainly surprising to find a study with four primary end-points. It would be interesting to know what was the accepted level of statistical significance for each one of the four primary end-points. On the other hand, the results of the study do not concur with those expressed by Dr Cannon. In reality, regarding the primary end-points, enoxaparin was only better than tinzaparin in the recurrence of unstable angina at 7 days. No statistical significant differences were observed between the two treatment groups with respect to death, myocardial infarction or refractory angina.

Although it is true that compared with unfractionated heparin no benefit was seen with either dalteparin in the FRIC study[3] or nadroparin in the FRAX.I.S. study[4] (whereas enoxaparin was superior in the ESSENCE[5] and TIMI 11B[6] studies) some possible explanations should be discussed.

In the FRIC[3] and FRAX.I.S.[4] studies, LMWHs were administered during the same period of time: 6 and 6 ± 2 days, respectively, whereas results for the primary outcome at day 8 in the TIMI 11B study[6] were derived from a comparison of enoxaparin administered for 8 days with UFH administered for 3 days, as remarked upon by Eikelboom et al.[7]. This difference in treatment duration could bias the results in favour of enoxaparin. In the ESSENCE study[5], there was a greater reduction in the composite primary outcome after stopping treatment than during active therapy. This late difference was driven primarily by a difference in the rate of recurrent angina. In the opinion of some authors[8], this pattern lacks biological plausibility and may well reflect the play of chance. Besides, median duration of treatment was 2-6 days. In reality, there is no evidence that such a short duration of treatment with UFH is effective in the treatment of unstable angina or myocardial infarction without ST-segment elevation. Moreover, in the study by Holdright et al[9], in which duration of treatment with UFH was 48 h, differences in outcomes between UFH plus aspirin and aspirin alone could not be demonstrated. Thus, the clinical statement that enoxaparin is more efficacious than UFH administered over 2-6 days is problematic.

Lastly, concerning the aPTT control achieved in clinical trials of enoxaparin vs UFH, it should be taken into account that in more than 40% of patients in the ESSENCE study[3] and in more than 50% in the TIMI 11B study[6] aPTT values were not in the therapeutic range. It seems that control of treatment with UFH was not optimal in these studies. A subgroup analysis of TIMI 11B[9], referring to the aPTT levels achieved with UFH, indicates that there is doubt that treatment with enoxaparin results in a better clinical outcomes for patients compared with every level of anticoagulation. A statistically significant benefit in favour of enoxaparin was obtained only in patients with an aPTT >85 s, when the targeted aPTT was 55-85 s. It is difficult to find an explanation for the superiority of enoxaparin in these patients and not in those with an aPTT in the therapeutic (or infra-therapeutic) range.

It is important to consider the above factors since they may influence the evaluation of the clinical benefit obtained with enoxaparin in unstable coronary artery disease.

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References


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subgroups, we found that the effects were not homogeneous. For example, the effect was greater in men than women, at older compared to younger age, at ST-depression at admission and if biomarkers indicating myocardial damage or inflammation were present\cite{1,3–5}. Based on a multivariate analysis we have therefore constructed a risk-scale and have been able to show that patients with three of the following risk factors; age >70, male gender, diabetes, earlier myocardial infarction, ST-depression at admission, troponin increase at admission, increased CRP or IL6 at admission have the greatest benefit of treatment regarding survival and reduced risk for myocardial infarction\cite{4–6}.

We did not perform any analyses of retrospectively identified small subgroups or eventual effects by deleting various patients, as such manoeuvres completely lack value. The occurrence of heterogeneity in subgroups of the material should be based on whether the risk-ratio points in the same direction as the main results. At such subgroup analyses, the confidence interval for risk-ratio will often exceed 1.0 (with the significance level for subgroup analyses being \(P > 0.05\)), which illustrates that the interpretation regarding subgroups is uncertain. As long as the subgroup risk-ratio points in the same direction as the main results and as long as the confidence interval does not differ from the rest of the material the most certain conclusion is that the results in the subgroup do not differ from the main results.

The health economic evaluations in FRISC II are prospectively planned. The cost-effectiveness analyses we did, and will do, are based on the study groups defined in the study protocol. The reasons why subgroup analyses cannot be done in the main study holds also for the health economics part of the FRISC II study. The strength of the economic study is that it is strictly prospective and analysed according to the protocol. Any deviation from this is a violation of good clinical trial practice and science. Incremental cost-effectiveness analyses are not meaningful in those cases where treatment effects are lacking. Thus it is not possible to calculate any cost-effectiveness ratios for the 3 months long-term treatment in the medical part of FRISC II.

The long-term cost-effectiveness regarding early invasive therapy in patients with unstable coronary disease remains to be seen. We are currently analysing the 24 months cost-effectiveness including quality-adjusted life years and lifetime costs.

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References


