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LETTERS TO THE EDITOR

Limitation of vWf Meta-Analysis in LMWH Comparison

Differences in clinical efficacy between unfractionated heparin (UFH) and low molecular weight heparin (LMWH) but also between several LMWH preparations are a hot topic in research due to differences in study results: enoxaparin proved superiority over UFH (1,2), whereas dalteparin and nadroparin showed only equivalence (3,4). As there is a lack of trials directly comparing LMWHs, some investigators tried to answer the question for the most effective LMWH preparation with data from comparative meta-analysis: Montalescot et al. (5) published a post hoc analysis in *JACC* in which they postulated differences between dalteparin and enoxaparin concerning their action on circulating von Willebrand factor (vWf) levels in patients with unstable angina. This could be of clinical importance as vWf has been shown previously to be a predictor of outcome in acute coronary syndrome (6). However, in scrutinizing the analytical method in Montalescot's work, serious drawbacks are revealed.

Montalescot et al. (5) presented a post hoc analysis that investigated, in part, results from two prospective trials with enoxaparin (1,2), one prospective trial with PEG-hirudin (PEGHIRUD 022) and one registry with dalteparin (USIC registry). A point of criticism is the comparison of prospective studies with a registry especially if randomized prospective data are available (3).

In addition, the levels of vWf on UFH treatment in this meta-analysis were obtained by pooling data from the mentioned studies. These pooled UFH data were compared with the LMWH results of the individual studies and the registry, respectively. This is a questionable procedure and weakens the results. The proper way would have been to compare the pooled UFH data with pooled results from all cited LMWH studies.

Finally, p values were only calculated for the comparisons of vWf levels between enoxaparin and, respectively, dalteparin and UFH, but not directly between the LMWHs themselves, which is, of course, impossible regarding the chosen analytical method. Only direct comparisons (also of other surrogate markers) could provide this data.

In our opinion, it is not correct from a scientific point of view to draw any conclusions concerning the relative efficacy of dalteparin and enoxaparin from these results. Although a proper post hoc analysis can be a helpful tool in certain cases, the question for the most effective LMWH should preferably be answered by head-to-head studies. If these studies are not available (e.g., because of cost reasons), the investigation of surrogate markers of hemostasis could be feasible to predict clinical outcome and to compare different LMWH preparations.

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REPLY

Interestingly, Dr. Hödl has focused his attention only on the two low molecular weight heparin (LMWH) treatments, whereas four anticoagulant treatments were examined in our study. Clearly, Dr. Hödl drew more definite conclusions than we did between the two LMWHs, because we were cautious enough not to compare dalteparin to enoxaparin (see Fig. 1 in Ref. 1), and we only compared each new anticoagulant treatment (enoxaparin, dalteparin, PEG-hirudin) to the standard of care—unfractionated heparin (UH) (1). Also, UH was the control arm in all the randomized studies in which our patients were included. Moreover, Dr. Hödl did not consider our warning (pg. 113 of Ref. 1) stating that "the main limitation of our study is the lack of randomization among the four treatment groups."

Dr. Hödl discussed post hoc analyses but forgot to mention and to refer to the first demonstration of von Willebrand factor (vWf) as a prognosis factor of outcome in unstable angina with a significantly better effect of enoxaparin compared to UH in controlling the release of vWf. These data were obtained in a prespecified substudy of the ESSENCE trial performed in several French centers; in a double-blind fashion, patients were randomized to receive either enoxaparin or UH. All clinical events were adjudicated by the end point committee of the ESSENCE trial; the substudy was designed and conducted prospectively, and all samples from all centers were analyzed in a blinded fashion in a central laboratory (2). Dr. Hödl suggests using data from the randomized FRIC trial opposing dalteparin to UH, which was published in 1997 (3); we would be very happy to collaborate with him on this great idea and test the vWf hypothesis in the FRIC population. Paradoxically, Dr. Hödl also states that the "proper"

way to analyze our data would have been to pool all the data obtained with the two different LMWHs; major chemical, biological and clinical differences exist between these LMWHs, and there has been much debate on this issue. We believe that pooling these data would have generated many more letters to the editor!

There are few biological markers of prognosis in unstable angina. Our recent studies have focused attention on vWf as a new marker of potential interest in acute coronary syndromes. It appeared consistently as a predictive factor of outcome, and we believe it deserves attention and further evaluation in large studies. Our most recent publication demonstrated that the new anticoagulants tested in unstable angina behave better than UH with regards to vWf release. We agree it should also be confirmed. Step-by-step we are progressing in the understanding of the role of vWf in the prognosis of unstable angina, and the time has come for head-to-head comparisons between the new anticoagulant treatments. In that regard, the ARMADA study has now been completed and we will share the data very soon. I am sure that Dr. Hödl will appreciate the results.

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Enoxaparin for Acute Coronary Syndromes?

Goodman et al. (1) conclude that enoxaparin is a more effective antithrombotic treatment than unfractionated heparin (UFH) for the prevention of rebound ischemia in patients with unstable angina or non-Q-wave myocardial infarction. We suggest an alternative conclusion.

Enoxaparin's plasma half-life is two to four times longer as compared to UFH after subcutaneous administration (2), even more when compared to UFH given intravenously, as in the Goodman et al. study. Activity against factor Xa and thrombin disappears only after more than 16 h (3), following moderate doses of enoxaparin. With high doses, as used in the ESSENCE study (1), enoxaparin's plasma half-life is substantially longer (4).

Therefore, after stopping study drugs in the ESSENCE study, enoxaparin's antithrombotic effect very likely lasted much longer than that of UFH. After stopping UFH, ischemic events during the 48-h monitoring period were twice as frequent as after stopping enoxaparin (45% vs. 26%), whereas there was no difference while on active treatment (25%)—compatible with an antithrombotic effect lasting about one day longer after enoxaparin. In addition, enoxaparin's antithrombotic effect wanes much more slowly as compared to IV UFH. This may have added benefit by attenuating a heparin rebound effect.

It remains to be convincingly shown whether enoxaparin or other low-molecular-weight heparins exert superior antithrombotic effects as compared to UFH. Superior clinical benefit might be explained by pharmacokinetic differences only. For patients with acute coronary syndromes, extending the duration and slower weaning (5) of IV UFH may well be better and cheaper.

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REPLY

Pechlaner et al. suggest that our findings (1) of less rebound ischemia with enoxaparin as compared to unfractionated heparin (UFH) are simply due to the longer half-life of enoxaparin. However, the ischemic episodes (average number and duration) identified during continuous electrocardiographic monitoring were statistically significantly lower in the enoxaparin as compared to the UFH group not only during the first 12 h after drug discontinuation but also during the >12 to 24-h and even the >36 to 48-h time intervals. This suggests that the benefit seen with enoxaparin is not simply due to prolonged half-life and greater anti-Xa:IIa activity that "wanes" more slowly than UFH. Indeed, there is growing evidence supporting additional mechanisms of benefit of enoxaparin over UFH beyond the differences in pharmacokinetics; for example, the significant blunting of the rise of von Willebrand factor with enoxaparin in the first 48 h of treatment (2).

As we noted, our substudy (1) was stopped at the time of overall trial completion but prior to enrollment of an adequately powered sample size to confidently address the initial 48-h period of active