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).

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. 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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REFERENCES


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