LETTERS TO THE EDITOR

Rebuttal of: "Can Home Prophylaxis for Venous Thromboembolism Reduce Mortality Rates in Patients With Chronic Obstructive Pulmonary Disease?"

To the Editor: We read with interest the report by Modesto-Alapont et al,[1] aimed at testing the efficacy of home heparin prophylaxis for reducing the incidence of venous thromboembolism (VTE) and the overall mortality rate in patients with severe chronic obstructive pulmonary disease (COPD). Eighty-seven inpatients with exacerbation of COPD were randomized at hospital discharge to receive either a low-molecular–weight heparin (LMWH), subcutaneous bemiparin 3500 IU/d for 6 months or no treatment. The study objective was really commendable. However, its methods were not appropriate for reaching the aims intended, as will be discussed below.

This was not a double-blind study, and no blinded assessment of outcomes was performed. In this case, a double-blind design could have been obtained by adding a simple daily placebo injection in the control group.[2] No data are given regarding inpatient prophylaxis before randomization or on the reasons for admission, which might have influenced the outcome in each group.

Sample size calculation was based on the very optimistic assumption that bemiparin would reduce the 6-month mortality by 75% (relative risk of death: 0.25). Twenty percent of deaths were assumed to occur in the untreated patients, and only 5% in the bemiparin group, at 6 months. According to the literature, approximately 10%-12% of deaths in medical patients are related to VTE[3] and approximately 33% of autopsies in medical patients show concomitant VTE.[4] This means that even if bemiparin had reduced all VTEs at autopsy, whether related or unrelated to death, the 100% reduction in VTE would represent a relative risk reduction in mortality ranging from 10% to 33%, but not up to 75%. According to our calculations, the sample size needed to show a 10% relative risk reduction in mortality is 12 078 patients, or 1230 patients if the expected relative risk reduction is 33% (2-sided χ^2 test; $\alpha=0.05$; power =0.80). Bemiparin has shown beneficial effects in experimental asthma,[5] which may have positive features in patients with COPD. Unfortunately, the effect of LMWHs on reducing COPD-related deaths is not known. Nevertheless, the relative risk reduction in mortality afforded by bemiparin versus no treatment in the study by Modesto-Alapont et al[1] was as high as 56%, yet not statistically significant ($P = .23$), mainly because of the sample size. According to our calculations, only 143 patients per group would have been required to show statistically significant differences in mortality between bemiparin and no treatment assuming a relative risk reduction in mortality of 56%. Nevertheless, we think that a more conservative assumption of treatment effects should be used for sample size calculation in subsequent studies.

No data are provided on the clinically suspected or autopsy-confirmed causes of death. The lack of autopsy data is a very weak aspect of the design of this study, since mortality was the main outcome measure. Lack of confirmation or elimination of pulmonary embolism (PE) as the cause of death may have important implications for assessment of efficacy. Unless PE has been ruled out, it will be difficult to attribute any death to causes other than PE.[6] Clinical signs of PE may be confused with an exacerbation of COPD symptoms. Clinical features such as cyanosis, dyspnea, tachycardia, and hypotension should be documented to allow for an assessment of PE severity but are not sufficient for diagnosis because of lack of specificity and low sensitivity.[6] Diagnosis of PE could be based on any of the established confirmatory tests, such as ventilation–perfusion scans, pulmonary angiography, spiral computed tomography, magnetic resonance imaging, or autopsy in fatal cases. Doppler ultrasound has high sensitivity and specificity to detect proximal deep vein thrombosis (DVT), but not distal DVT. In the study by Modesto-Alapont et al[1] it is not clear whether the incidence of DVT detected by DUS represented proximal or distal symptomatic DVT, asymptomatic DVT, or all of them.

Major and minor bleeding is not defined in the study by Modesto-Alapont et al,[1] and it is therefore difficult to assess the true incidence of major and minor bleeding. Current guidelines of the International Society of Thrombosis and Haemostasis (ISTH) adopted by the European Medicines Agency (EMEA)[6] recommend the following criteria to define major bleeding in nonsurgical patients: fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of whole blood or red cells. The authors state in the conclusion that they "found a high prevalence of all types of bleeding." However, in the abstract and results section they state that all bleeding complications were mild bleedings or subcutaneous hematomas. Therefore, we suspect that no major bleeding events occurred with bemiparin and that no differences in major bleeding were found in their study as compared to the control group, as reported in the literature.[2] Finally, we think that, in this type of study, the reduction in VTE-related mortality should be weighed against a possible increase in deaths related to bleeding or other drug-related deaths, but not against an expected increase in mild bleeding or hematoma at the injection site.

In conclusion, the study does not allow for drawing any relevant conclusion because of the abovementioned methodological weaknesses. There was a trend toward a lower mortality rate in patients receiving bemiparin that was not significant because of the inadequate sample size used and, as expected, there was a higher incidence of mild bleeding complications with no increase in major bleeding rates in patients treated with LMWH as compared to those receiving no treatment. Further studies with an appropriate sample size and methodology will be needed to address this issue.

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