LETTER TO THE EDITOR

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The FENO-HSR study: details of statistical analyses

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Dear Editor,
One of the most life threatening complication in critically ill patients is acute kidney injury (AKI) and no drug has evidence based medicine to support its use to reduce the incidence of renal replacement therapy (RRT) or mortality in patients with or at risk for AKI. Fenoldopam reduces the risk of RRT (1,2) and in-hospital mortality (2) according to recent meta-analyses. We planned a large, multicentre, randomized, double-blind, placebo controlled clinical trial to confirm the fenoldopam beneficial effect on RRT (3) and we hereby describe in details the planned statistical analyses.
The recommendation of the Consolidated Standards of Reporting Trials (CONSORT) statement will be followed (4) and all data will be analyzed according to the intention-to-treat principle, beginning immediately after randomization. Data will be stored electronically and analyzed by use of SAS (version 9.2, SAS Institute Inc. Cary, NC, USA) and Stata (Stata Statistical Software: version 11, College Station, TX, USA). Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Unadjusted univariate analyses, to compare the two treatment groups, will be based on Chi-square or Fisher exact test. Relative risks and 95 % confidence intervals will be calculated by means of the two-by-two table method with the use of log-normal approximation. Continuous variables will be reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Between-group differences will be evaluated using the T test or Wilcoxon signed rank test, in accordance with the Shapiro-Wilk normality test. Data about primary and secondary endpoints will be reported also as relative risk and number needed to treat (95 % confidence intervals) or as difference between means with 95 % CI where appropriate.
Generalized regression models, adjusted for baseline values, will be used to estimate the treatment effect (and its 95 % confidence intervals) with respect to primary and secondary endpoints. Statistical significance will be set at the two tailed 0.05 level for hypothesis testing.
All data analyses will be carried out according to a pre-established analysis plan. In particular, the following planned subgroup analyses for a beneficial effect of the study drug on the primary end-point (RRT) and for survival will be performed: patients with severe congestive heart failure (New York Heart Association functional status III or IV); patients with peripheral vascular disease; patients who underwent mitral surgery for insufficiency (because of reduction of postoperative afterload with fenoldopam); patients who had hypertension or prehypertension (5) before surgery or before randomization; patients who had normal blood pressure (systolic blood pressure > 90 mmHg without a decrease of more than 40 mmHg from baseline) before randomization; patients who had low cardiac output syndrome

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or sepsis as major cause of AKI according to the physician; patients who had mechanical ventilation or cardiac support (IABP or inotropic score > 10) at randomization; patients who had serum creatininine values before surgery or before randomization < 1.5 mg/dl, patients less than 65 years old.

Furthermore, exploratory analyses will be performed in centers using the study drug for at least 24 hours with a dose > 0.1 µg/kg/min.

Following an Ethical Committee request we will perform a third, unplanned ad interim analysis at 667 patients to address safety issues in a setting (AKI) with high mortality rate. Data evaluation at ad interim analysis will be based on the alpha spending function concept, according to Lan and DeMets (6), and will employ O'Brien-Fleming Z-test boundaries (7).

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