Reviewer's report

Title: Dose Dependent Effect of Statins on Postoperative Atrial Fibrillation after Cardiac Surgery among Patients Treated with Beta Blockers

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Reviewer: Giovanni Mariscalco

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In their present study Mithani and Colleagues analyse the effect of preoperative statins on atrial fibrillation (AF) after cardiac surgery. Data were retrospectively acquired and 1936 patients were enrolled (about 90% of patients was administered Simvastatin). Postoperative AF occurred in 31% taking statins compared to the 29% ones without them (P=0.49). In multivariable analysis statin use was not associated with a postoperative AF reduction (OR 0.93; 95%CI 0.7-1.2). Only patients with a Simvastatin dose > 20 mg/daily revealed a 36% reduction in the risk of developing the arrhythmia.

Certainly, because of the increased morbidity and mortality associated with AF after cardiac surgery, the effectiveness and usefulness of drug prophylaxis is an issue to be addressed. In addition, the preventive statin effect on postoperative AF is a debated topic. However, the manuscript reveals serious and remarkable concerns about the study design and statistic. The data analysis does not support Authors’ conclusions, and the results obtained are not connected with a lack of statin activity but rather with the study limitations.

Major Compulsory Revisions

Baseline differences between patients taking statins and patients without them are evident and no explanation are provided. Diabetes, body mass index, left ventricular function, previous myocardial infarction are well known risk factors associated with postoperative AF. All these variables are not balanced between the two groups. In order to adjust for these relevant differences, the Authors should have explored the use of propensity matching. The adopted logistic regression model is of questionable value. The statement “this large sample afforded us a greater statistical power to adjust for all of the measured differences between the statin vs. no-statin groups” is not justified by the statistical analysis carried out. Why did not the Authors provide all the significant variables obtained after multivariable analysis? In the model, did the Authors consider the Simvastatin dose as a dichotomous variable? Did the Authors also analyse the possible effect of preoperative statin treatment on AF development?

Another interesting issue is the lack in the statistical and descriptive analysis of common variables associated with postoperative AF (inotropic support, atrial volume). Because the Authors remarked as a strengthened element of their manuscript the analysed effect of statin in valve surgery patients, why did the Authors not include the atrial volume as a variable in the multivariable approach?
Why had the Authors only males as enrolled patients? Is the Authors’ Hospital a heart centre only for male cardiac surgery patients? Gender is a well known factor influencing postoperative AF occurrence. It seems that the enrolled population does not reflect the normal cardiac surgery population.

Is not clear to me how the Authors can affirm that “when beta blockers are on board, higher doses of statins were required to reduce the incidence of postoperative AF”. First, their statistical analysis was not conceived for exploring this issue. Possible statistical interaction between beta blockers and statins were not explored at all. The same for the statement, “the incidence of postoperative AF was not influenced by statin treatment in the overall study cohort the statement”. How can the Authors state in the next sentence “however, there was a 34% reduction in postoperative AF among those who were treated with a higher dosage of Simvastatin?” Both conclusion and study end-point are unclear.

Another issue to be clarified by the Authors is the extensive postoperative use of beta blocker and how this administration can interfere with the possible statin effect. The fact that Simvastatin > 20 mg/daily is effective against postoperative could simply mean that the dosage for the Simvastatin prophylactic AF effect can be found only with consistent dosage.

**Level of interest:** Reject as not of sufficient priority to merit publishing in this journal

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.