Author’s response to reviews

Title: Hemodynamic Effects of Peri-Operative Statin Therapy in On-Pump Cardiac Surgery Patients

Authors:

Jose Hinz (jhinz@med.uni-goettingen.de)
Philipp Gehoff (philipp.gehoff@gmx.de)
Hanna Schotola (hschotola@med.uni-goettingen.de)
Morteza Tavakkoli Hosseini (morteza.tavakkoli@gmail.com)
Vassilios N Didilis (vidilis@med.duth.gr)
Fawad A Jebran (ajebran@med.uni-goettingen.de)
Anastasia Gehoff (Anastasia.Gehoff@gmx.de)
Christoph H Wiese (cwiese@med.uni-goettingen.de)
Egbert G Schulz (EGS@dialbov.de)
Friedrich A Schoendube (schondube@med.uni-goettingen.de)
Aron F Popov (popov@med.uni-goettingen.de)

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Author's response to reviews: see over
Dear Editor,

Thank you very much for the revision of our manuscript. We enjoyed yours and the remarks of the reviewers, which improves our manuscript, and responded them point-by-point. Changes in the manuscript are marked in red color. Hoping that the present paper will be suitable for publication we thank you in advance for the time spent in revising the manuscript.

Best regards

Aron-Frederik Popov
Reviewer's report

Title:
Hemodynamic Effects of Peri-Operative Statin Therapy in On-Pump Cardiac Surgery Patients

Version: 1
Reviewer I: Radke
Reviewer's report:
Specific comments

1. The authors conducted an extensive accumulation of perioperative data on an impressive number of patients. Simply comparing the predictors per group doesn’t do this effort justice. A more detailed analysis such as a regression analysis or even a propensity score analysis aimed at a solid primary outcome could potentially yield more robust results.

AW:
The propensity score is used to reduce selection bias by equating groups on covariates which might influence the result. Therefore it is necessary to select the patients in advance regarding the covariates (e.g. different statin drugs and dosages) to avoid any bias. However, this tool is only useful in a prospective study design and it is therefore not suitable for our retrospective observational study. We were aware about this limitation which can lead to less robust results and therefore we have already performed a multivariate analysis for the different statins drugs and dosages (page 8), which revealed no significant differences at all. For more clarification we highlight it in the result section, page 8 with additional information.

“The different statin drugs and dosages did not influence the perioperative mortality in our study group at all in a multivariate analysis.”

Moreover, the second reviewer stated that there is no need to use additional statistics.

2 Page 5: The authors state that this was a retrospective study, but “patient approval was obtained BEFORE participation”. Please clarify.

AW: These patients collective were part of a former prospective study and we consented them for more studies. We included in the methods section “The investigated patients were part of former prospective study.”

Page 5: Was the study approved by the local ethics committee?
We already mentioned that in the methods section “The retrospective single centre study was approved by the ethics committee of the Medical Faculty, University of Göttingen, Germany”
The study included 478 patients during a 12 month period. What were the in- and exclusion criteria?

AW

Inclusion criteria:
Adult patients undergoing cardiac operation with cardiopulmonary bypass were included.

Exclusion criteria:
Patients aged >80 and known neoplasms were excluded from this study.

How were the risk factors defined (hypertension, diabetes, positive family history, peripheral artery disease, neurocerebral events, COPD, renal dysfunction etc.)?

AW:
These risk factors were obtained from patient’s history and from doctor’s letters.

Page 6: What were the primary and secondary endpoints?

AW:
The primary endpoint is the hemodynamic effects of peri-operative statin therapy in on pump cardiac surgery patients, and the secondary endpoint is the hospital mortality.

Page 6: The use of tests is not appropriate: The Student’s T would be appropriate for scaled variables, not Fisher’s exact test. Fisher’s is appropriate for categorical variables.

AW:
We changed the statistic analysis section due to our accidentally mistake.

“Comparisons of categorical scaled variables for patients with and without preoperative statin therapy were made with Fisher’s-Exact-Test and ordinal variables were compared with Student’s-T-test.”

Page 6: The statistics section mentions a multifactorial analysis, but no details. There are no results of this analysis presented or discussed.

AW:
We mentioned in the manuscript that even a multivariate analysis revealed no statistical significance. Therefore, we wanted to avoid providing the readership with redundant informations regarding that topic.
From the data one cannot deduce that statin use did not influence mortality, only that you saw no association. Was the power of the study adequate to detect changes in mortality?

**AW:**
The calculated appropriate sample size needed to attain a given power of ~80% and to achieve a significance in mortality of p<0.05 was 500 patients.

Page 9: “quite uniform” is very vague, please rephrase.

**AW:**
We changed in the result section the last sentence. “Also, there was no statistical difference in length of stay in intensive care unit, hospital stay and mortality.”

Page 12: “The data of this study showed that there was no benefit …” is not supported by the results and the analysis. However “The results of this study do not support a benefit in perioperative statin therapy…” would be valid.

**AW:**
We followed the advice of the reviewer.

“The data of this study do not support a benefit in perioperative statin therapy for patients undergoing on-pump cardiac surgery, in terms of postoperative hemodynamic improvement or clinical outcome.”
The premise for the current study is based on the belief that statins have pleiotropic properties that contribute to a decrease in systemic inflammation. The authors hypothesized that patients treated with statins could have less inflammation after surgery and therefore less vasodilation and altered hemodynamic parameters postoperatively. Does any experimental laboratory or animal data exist to support this hypothesis that statins can impact hemodynamic parameters in the presence of an inflammatory process?

AW:
To our knowledge there is currently no animal model published in terms of inflammation combined with hemodynamics. However, as we mentioned in the introduction there are several reports, that statins can reduce the inflammation after on pump cardiac surgery. Moreover, it is well known that inflammation can lead to hyperdynamic circulation, which is common in SIRS and can have influence on postoperative course in terms of hemodynamics. Currently, there is no proven evidence that statins can influence in a clinical setting the hemodynamics and therefore this was the aim of our study which we already mentioned in the introduction.

The authors compared hemodynamic parameters between patients who did and did not receive “perioperative statins”. How exactly did the authors define perioperative statin therapy? i.e. 48 hours before surgery? 1 week before surgery? statin therapy within 24 hours after surgery? This needs to be clarified in the Abstract and Methods.

AW:
“statin-patients” which underwent an elective cardiac surgery received at least 6 weeks prior surgery their drug continuously and this therapy was not interrupted till discharge.
The authors state in the Abstract and Methods that “categorical variables were compared with Student T tests”. The term “categorical” should be changed to “continuous”.

AW:
We changed the statistic analysis section due to our accidentally mistake.

“Comparisons of categorical scaled variables for patients with and without preoperative statin therapy were made with Fisher’s-Exact-Test and ordinal variables were compared with Student’s-T-test.”

Outside of a randomized trial, it is difficult to compare hemodynamic parameters in an observational study such as this one since there are so many confounding variables which are nearly impossible to control for, even if sophisticated statistical techniques are used. Factors such as preoperative antihypertensive medication use (i.e. ACE-inhibitors) and postoperative vasopressor/vasodilator use strongly interfere with the objective of evaluating the hemodynamic impact of statin therapy after cardiac surgery

AW:
Thank you very much for this important comment. We also took this in consideration in our manuscript in the discussion section and in the limitation section.

“We suppose that increased ACE inhibitor treatment in the statin group might have influenced our study outcome. Boeken et al. pointed out that long-term treatment with ACE inhibitors caused vasodilatatory effects and enhanced perioperative need for catecholamines. Furthermore the ACE inhibitor induced vasodilatation could be…..”

“Therefore it does not seem to be very surprising that the statin group is dominated by Coronary artery bypass graft (CABG) patients, whereas the no-statin group consists of patients with valvular heart disease with or without coincident coronary disease. The cardiovascular pathophysiology of these two groups is entirely different. This can have potential influence on perioperative haemodynamic data…..”

The Discussion section is disorganized and difficult to follow. It is poorly written. A number of spelling and grammatical errors needed to be corrected.

AW: The discussion section was re-structured and the spelling and grammatical errors are corrected.