Author's response to reviews

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

Authors:

Salima Mithani (salima.mithani@va.gov)
Muhammad S. Akbar (muhammad.akbar@va.gov)
Deborah J Johnson (deborah.johnson5@va.gov)
Michael Kuskowski (michael.kuskowski@va.gov)
Katherine K Apple (katherine.apple.1@gmail.com)
Jana Bonawitz-Conlin (jana.bonawitzconlon@va.gov)
Herbert B Ward (wardx020@umn.edu)
Rosemary F Kelly (kelly071@umn.edu)
Edward O McFalls (mcfal001@umn.edu)
Hanna E Bloomfield (hannah.bloomfield@va.gov)
Jian-Ming Li (jian-ming.li@va.gov)
Selcuk Adabag (adaba001@umn.edu)

Version: 3 Date: 8 October 2009

Author's response to reviews: see over
October 5, 2009

Vipin Zamar, MD
The Journal of Cardiothoracic Surgery Editorial Team

Dear Dr. Zamar,

Enclosed is our revised manuscript, “Effects of Statins on Atrial Fibrillation after Heart Surgery in Patients Treated with Beta Blockers” which we submit as an original research article for consideration for publication in the Journal of Cardiothoracic Surgery.

We have revised our manuscript based on all four reviewer comments. We appreciate their constructive comments and believe that our paper has been strengthened as a result. Please find below point by point response to all the concerns and questions raised by the reviewers. Our response to each reviewer starts on a separate sheet.

Please direct correspondence to: A. Salima Mithani, MD
Veterans Affairs Medical Center
Emergency Department
One Veterans Drive
Minneapolis, MN 55417
Tel: 612/467-2792
Fax: 612/467-2270
Email: salima.mithani@va.gov

Thank you for your consideration.

Sincerely,

A. Salima Mithani, MD.
Responses to Referee Cengiz Ermis

We appreciate the constructive comments made by the reviewer and we revised the manuscript accordingly. As a result, we believe our paper has been strengthened considerably.

**Comment 1:** Why did most of the patients take simvastatin rather than other statins?

**Response:** The majority of our patients were taking Simvastatin because this medication has been the preferred statin on the formulary of the Minneapolis VA Medical Center.

**Comment 2:** Would a dose of 20mgs be a real cutoff point to discriminate small and large dose levels for a statin like simvastatin?

**Response:** The reviewer raises an important point. Indeed, a higher dosage of Simvastatin may be needed to achieve equivalency with some of the more powerful statins. In this study, we used Simvastatin 20 mg in our dosage analyses because as this was the median statin dose in our population. There weren’t sufficient number of subjects to evaluate higher cutoff simvastatin dosages.

**Comment 3:** Any data on left atrial diameter comparisons between patients who went into AF and who did not?

**Response:** We agree with the reviewer that left atrial size is an important predictor of atrial fibrillation. However, we did not have access to these data in the present investigation. Left ventricular systolic function was the only echocardiogram parameter included in this study.
Responses to Referee Mehmet Aktas

We appreciate the constructive comments made by the reviewer and we revised the manuscript accordingly. As a result, we believe our paper has been strengthened considerably.

Comment 1: The word "statin" is sometimes capitalized and at other times it is not. It does not need to be capitalized.

Response: We have revised the manuscript in accordance with the reviewer’s comment. The word “statin” is now spelled in lower case letters throughout the manuscript.

Comment 2: No mention of post-op antiarrhythmic drug use, type, frequency etc

Response: The reviewer brings up an important point, which we would like to clarify. Except beta blockers, no antiarrhythmic agents are started *routinely* in the post-operative period at our medical center. In cases who develop atrial fibrillation, antiarrhythmic agents are initiated at the discretion of the attending physician. However, such practice would not affect the results of our study, since the antiarrhythmic agent would have been started *after* the development of atrial fibrillation. In our study cohort 16% of the subjects were taking Amiodarone preoperatively, which was continued in the postoperative period. However, there was no interaction between Amiodarone and statin-effect on atrial fibrillation. We hope this clarification is satisfactory to the reviewer.

Comment 3: Statins have anti-inflammatory properties hence there use in the post cardiac surgery state may not have affected the incidence of AF but could it have decreased the overall
burden of AF. Data on what was done to these patients with AF would be interesting, i.e. how many converted spontaneously? How many required DC cardioversion? How many were left in AF?

**Response:** We agree with the reviewer that statins may have reduced the total burden of atrial fibrillation. However, the present study was designed to assess the incidence of atrial fibrillation in this post-surgical cohort. As such, patients were censored after developing atrial fibrillation. Although we agree that the management of patients *after* atrial fibrillation is important, we believe that this information is beyond the scope of this paper.
Responses to Referee Giovanni Mariscalco

We appreciate the many constructive comments made by the reviewer and we revised the manuscript accordingly. As a result, we believe our paper has been strengthened considerably.

Comment 1: Baseline differences between patients taking statins and patients without them are evident and no explanation is provided.

Response: The reviewer is correct that the statin-treated and untreated groups have differences in baseline variables, displayed explicitly for the reader in Table 1. The majority of the differences between the study groups, in fact, reflect the differences between the CABG vs. valve surgery patients. Whereas statin-treatment is initiated by their physicians in the majority of patients undergoing CABG due to the ischemic nature of their disease, this is not the common practice for valve surgery patients without ischemia. In the design phase of our study, we made a conscious decision to include all cardiac surgery patients (vs. patients undergoing CABG only) because 1- previous studies did not include a sufficient number of these patients and 2- to include a cohort that reflected a real-world cardiac surgery patients. Having baseline differences between the study groups is an inherent problem of all observational studies, such as the present study, only solved by a randomized clinical trial design, which this study does not claim to be. To limit the effects of the baseline differences on the study outcome, we accounted all baseline differences in our analyses (page 5 and lines 12-19) “Multivariable logistic regression models included the baseline differences between the statin and non-statin groups and predictors known to be associated with postoperative AF. Thus the predictor variables in our multivariable models were age, body mass index, prior history of AF, chronic lung disease, diabetes mellitus, hypertension, left ventricular function, peripheral and cerebral vascular disease, smoking status,
history of myocardial infarction, New York Heart Association functional class, beta blocker treatment status, calcium channel blocker treatment, digoxin treatment, cardiomegaly, surgical procedure, cross-clamp time and statin treatment status”.

However, we are aware that bias among study groups cannot be completely accounted for by statistical analysis alone. Indeed, there are frequently unmeasured or unknown differences between groups, only abolished by randomized clinical trials. Therefore, we duly accepted this limitation in our manuscript. (Page 10 and Lines 9-12) “…this study also has some limitations. The inherent short-comings of retrospective cohort study design, including baseline differences among study groups, cannot be completely avoided, by a large sample size and statistical adjustment for the multiple variables.” We hope that the reviewer finds this genuine effort to reduce the noise and explicit attitude to accept limitations satisfactory.

Comment 2: 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.

Response: As noted above, the baseline differences between the two groups, including the variables selected by the reviewer, were adjusted for in the multivariable logistic regression model. A full list of the variables included in our logistic regression models is displayed for the reader in the Data Analysis section (page 5 lines 12-19) of the manuscript. Further, in
accordance with the reviewer’s suggestion we have explored the use of propensity matching. A propensity score for taking statin was created for each patient using the variables that were different between the statin-treated and untreated groups as listed in Tables 1 and 2. In multivariable analysis, including the propensity score, (other variables age, diabetes mellitus, COPD, smoking status, peripheral arterial disease, prior MI, NYHA class, prior AF history, cardiomegaly, postoperative beta blocker use, estimated mortality risk, medications and the surgical procedure) statins reduced AF incidence at high but not low dosages (odds ratio 0.76; 95% confidence interval 0.6 to 0.97; p=0.03). These results are very similar to those we had originally reported. We have now included these additional analyses and the results in our manuscript.

Page 5 lines 19-22 “As a separate analysis a propensity score for taking statin was created for each patient using the variables that were different between the statin-treated and untreated groups. Multivariable models including the propensity score were created to assess the statin effect on AF.”

Page 7 lines 9-11 “Results were similar after performing propensity matching analysis, to adjust for baseline differences between the statin-treated and untreated groups.”

**Comment 3:** Why did not the Authors provide all the significant variables obtained after multivariable analysis?

**Response:** Predictors of postoperative AF are displayed on page 6 lines 20-23 “Postoperative beta blocker use (p=0.01), cardiomegaly (p=0.01), and previous history of AF (p=0.001) were associated with AF. Patients with a previous history of AF had a 5 times higher incidence of
postoperative AF (odds ratio 5.1; 95% confidence interval 3.4 to 7.7; p <0.0001) compared to those without a prior history.”

**Comment 4**: In the model, did the Authors consider the Simvastatin dose as a dichotomous variable?

**Response**: Indeed, Simvastatin dosage was a dichotomous variable, separated at the median dosage (i.e 20 mg) in our study cohort. Low numbers did not allow evaluation with other specific dosages.

**Comment 5**: Did the Authors also analyse the possible effect of preoperative statin treatment on AF development?

**Response**: In this study, all of the patients in the statin group were taking these medications preoperatively. Statins were *not* initiated postoperatively in any patient. This point has been clarified for readers in the manuscript (page 6 and line 9): “A total of 1322 (68%) patients were treated with statins pre- and postoperatively.”

**Comment 6**: Another interesting issue is the lack in the statistical and descriptive analysis of common variables associated with postoperative AF (inotropic support, atrial volume).

**Response**: The reviewer raises an important point. Inotropes were used, beyond the first 24 hours after surgery, in only in 20 patients. Excluding these patients from the analysis made no difference. Left atrial volume is an important predictor of atrial fibrillation. However, we did not have access to these data in the present investigation.
Comment 7: 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?

Response: We agree with the reviewer that left atrial size is an important predictor of atrial fibrillation. However, we did not have access to these data in the present investigation. Left ventricular systolic function was the only echocardiogram parameter included in this study.

Comment 8: 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.

Response: Our study was conducted at the Veterans Affairs (VA) Medical Center in Minneapolis, Minnesota. VA hospitals serve veterans of U.S. military. Thus, 99% of our patient population is male. We had acknowledged this point among the limitations (page 10 and lines 12-13): “Almost all of our study patients were male. Thus caution should be exercised in extending these results to women”.

Comment 9: 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.

Response: The reviewer is correct that we have not tested the statin effect among patients with and without beta blockers. We have modified our conclusions accordingly. Page 2 and lines 21-
Among cardiac surgery patients treated with postoperative beta blockers, Statin treatment reduces the incidence of postoperative AF when used at higher dosages. We hope that this is satisfactory to the reviewer.

**Comment 10:** 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.

**Response:** We agree that this statement, as it was written, may have caused confusion. Thus, we have revised this statement as follows (page 8 and lines 5-7) “There was a 36% reduction in postoperative AF among those who were treated with a higher dosage (i.e. > 20 mg/day) of statins. However the incidence of postoperative AF was not influenced by low dose statin treatment.”

**Comment 11:** 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.

**Response:** We are not entirely clear as to what the reviewer is referring to in this comment. The mechanisms of effect of statins on AF are speculative but may be secondary to their anti-inflammatory action. Whether higher dose of statins reflected more antiinflammtory effect in this study is unknown, as inflammatory markers were not followed. Whether there is an interaction
between statins and betablocker is also unknown since almost all of our cohort received postoperative beta blocker treatment
Responses to Referee Francisco Marín

We appreciate the constructive comments made by the reviewer and we revised the manuscript accordingly. As a result, we believe our paper has been strengthened considerably.

**Comment 1:** The authors should show the data together of CABG and valvular surgery.

**Response:** We indeed presented the combined data for both CABG and Valvular Surgery in the manuscript. A pre-determined subgroup analysis was performed to assess statin-effect with each type of surgery showed no difference. These results appear on Page 7 lines 6-12 of our manuscript: “In multivariable analysis, after adjusting for the differences between the statin and non-statin groups and for predictors known to be associated with postoperative AF (full list under statistical methods), statin treatment was not associated with the risk of postoperative AF (odds ratio 0.93, 95% confidence interval 0.7 to 1.2; p = 0.59). …..Results did not change when the analysis was limited to patients who underwent CABG only.”

**Comment 2:** Perhaps it could be more interesting to select only the patients under simvastatin (the great majority).

**Response:** As recommended by the reviewer, we re-analyzed our data limited to patients taking Simvastatin. The findings suggested that higher dose of Simvastatin ≥20 mg may reduce the incidence of postop Afib by 23% (odds ratio 0.77; 95% confidence interval 0.59 to 1.01; p: 0.06) The marginal P value is probably secondary to the smaller sample size in this sub group. We hope that this is satisfactory to the reviewer.

**Comment 3:** The authors have not compared patients under beta-blocker and not. So, they
should modify their conclusions.

**Response:** The reviewer is correct that we have not tested the statin effect among patients with and without beta blockers. We have modified our conclusions accordingly. (Page 2 and lines 21-22) “Among cardiac surgery patients treated with postoperative beta blockers Statin treatment reduces the incidence of postoperative AF when used at higher dosages” We hope that this is satisfactory to the reviewer.

**Comment 4:** It would be interesting to know, how long were the patients under statins.

**Response:** The reviewer makes an important point. Indeed, it is possible that the effects of statins on atrial fibrillation may depend upon the duration of statin treatment. We concede that this information was not available to us. We have now acknowledged this point as a limitation in our manuscript (page 10…lines 14-16): “Also, the duration of statin treatment was not known. It is possible that the effects of statins on AF is dependent upon the duration of statin-therapy.”