Author's response to reviews

Title: Statins in Candidemia: Clinical Outcomes From a Matched Cohort Study.

Authors:

Graeme N Forrest (forrestg@ohsu.edu)
Angela M Kopack (akopa002@umaryland.edu)
Eli N Perencevich (eperence@epi.umaryland.edu)

Version: 2 Date: 17 April 2010

Author's response to reviews: see over
Statins in Candidemia: Clinical Outcomes From a Matched Cohort Study.

Manuscript #: 1267562813328146

Reply to Reviewers:

To the editor:

We appreciate the thoughtful and thorough work performed by the reviewers. The following are the replies to the reviewers and corrections as requested.

Reviewer 1:

1) The references concerning the topic statin use and infection/sepsis prognosis should be updated. I noticed that results from the study were first presented at the ICAAC in 2006, and there have been several important studies in recent years. The authors should consider citing, and discussing in relation to their findings where appropriate, some of the following work:

Reply: Thank you for further references. We have reviewed these references and 3-4 were very pertinent to our results, especially severity of illness prior to ICU admission. We have included several of these references in the discussion of our results.

2) The matched cohort design can be defended as an appropriate choice. However, judged from Table 1, the groups are not really well matched on comorbidity, as claimed in the Methods. Please comment.

Reply: Every effort was made to find matching controls. However, it was not always possible. Major differences were that exposed patients on statins were more likely to have heart failure, renal insufficiency, stroke, and peripheral vascular disease. Since our hypothesis was that statins would be protective and statins had higher comorbidity, we expect this to bias our analysis to the null. Thus, if we were able to obtain perfect matching, we would have seen statins as more protective. We have added sentences to that effect in the Discussion section: “Major differences were that statin-users were more likely to have heart failure, renal insufficiency, stroke, and peripheral vascular disease. Since our hypothesis was that statins would be protective and statins had higher comorbidity, we expect this to bias our findings to the null. Thus, if we were able to obtain perfect matching, we would have seen statins as being more protective”

3) Moreover, the statistical analysis section is a bit unclear to me, as the authors state ‘bivariable comparisons’ several times without mentioning which variables are compared. Please clarify.

Reply: Bivariable comparisons are all of those that are not multivariable. This includes relationship between statin exposure and outcome mortality but also between statin exposure and potential confounders (Table 1) and models 1-6 in Table 3. As this is standard terminology, we will not make any changes in the manuscript.
4) Using statistical significance levels to choose potential confounders to include in a regression model is generally a bad idea for several reasons, in particular in a study with very small sample size like this (see for instance: Rothman KJ: Epidemiology – an introduction. Oxford University press, 2002, pp. 193-197). As p-values are a function of both the strength of association and the sample size, for covariates with low prevalences even large differences in the distribution between the statin/non-statin categories or outcome dead/alive would turn out to be statistically non-significant, and conversely, for covariates with high prevalence even very moderate differences according to statin use or mortality might turn out statistically significant. For instance, male gender is associated with highly (1.8 times) increased mortality (Table 3) but p-value 0.46 and therefore not included, whereas WBC count is associated with only 1.2 times increased mortality but p-value 0.08 and therefore included. Moreover, in order to influence the association between exposure and outcome a confounding factor must have an effect on the outcome, must be imbalanced between exposure groups and - importantly - cannot be an effect of the exposure. Levels of APACHE II, WBC count etc. may reflect anti-inflammatory effects of statins and should therefore not be controlled for (In other words: statins might lower mortality by lowering sepsis severity, APACHE II etc. – this effect may be obscured by adjusting for the variables).

I therefore strongly suggest starting with a very small set of clinically meaningful predictors of mortality (that is, predictors that are not intermediate steps in the causal pathway between statins and mortality such as acute disease markers). Most investigators would agree that age, gender and comorbidity are the most important potential baseline confounders. As statin exposure groups are well age-matched in the study, I think only male gender qualifies as predictor, and potentially an aggregate measure of comorbidity due to sample size considerations, e.g. history of any comorbidity ‘yes/no’. I would suggest omitting all markers of acute disease severity from the model, for reasons stated above, and aim to adjust for these two confounding factors in the model.

Reply: We thank the reviewer for their comments on analysis. We agree that selection of confounding variables to include in the multivariable analysis is important. However, given that we have so few patients and thus few outcomes, at most 2-3 variables could be included in the model. We forced statin exposure into the model and therefore, inclusion of other variables was limited to 1-2 other variables. In fact, we have now entered each variable into the model individually and left in Apache II since it was the variable that most significantly altered the OR of statin exposure. We have altered our statement in the methods to document that change.

As for male gender vs. WBC entrance into the model because of the size of the OR, we should clarify that the OR given for WBC is per 1 count of the WBC. If we dichotomized the WBC variable around a measure of central tendency (median or mean) the OR would likely be higher, but this would represent something of additional clinical importance. We believe variables should be left in the model not by the size of their individual OR but in how they impact the primary association under study: statins and mortality.
We disagree that WBC and APACHE II should not be included in the model. To exclude severity of illness from the model because of some theoretical causal pathway issue would be beyond the literature at this point. It is true that APACHE II would be associated with the outcome however patients are not treated with statins based on higher or lower severity of illness. We don’t feel treating severity of illness in the analysis as one would if looking at a therapeutic antibiotic is appropriate.

5. For frequent outcomes, such as death in this study, the odds ratio highly overestimates the relative risk for the outcome. The statement ‘91% reduction in mortality’ (page 6) may be inappropriate. Please comment in the paper.

Reply: This is an important point. OR can over-estimate the relative risk in this case. The RR=0.42 for mortality in Table 1 (27%/63%) is much less protective that the OR would suggest. We have added a comment in the discussion to that effect.

6. Several places in the paper, the terms ‘case and controls’, ‘case-controlled’ etc. are used. This is not appropriate, since the study is not a case-control study. The terms ‘statin users / statin-exposed’ and ‘non-users of statins /non-exposed’ should be used instead.

Reply: Agree with your suggestion and corrected throughout the paper.

7. would prefer not to do statistical testing (p-values) of whether the plain distribution of covariates differs between the categories of statin exposure in Table 1. As mentioned, p-values are a function of both the strength of association and the sample size; therefore, for covariates with low prevalences even large differences in the distribution between the statin/non-statin categories would turn out to be statistically non-significant, and conversely, for covariates with high prevalence even very moderate differences according to statin use might turn out statistically significant. Furthermore, the associations between the different covariates and statin use are likely to be heavily mutually confounded in crude analyses. The interpretation of p-values alone is therefore complicated and I feel that little information is gained.

Reply: We thank the reviewer for this comment. Since some readers prefer p-values in Table 1’s of papers, we will leave them in. If a reader chooses to ignore them, that is fine too.

8. Comorbidity: Please explain how this was assessed. Are the conditions displayed in Table 1 pre-admission chronic diseases? Or diseases diagnosed during hospitalization? Or are they the very reason for ICU transferral? These factors should be distinguished, if possible.

Reply: These are pre-admission chronic diseases, not reason for ICU transferral. We have include the age adjusted Charlson co-morbidity index for both groups. Have clarified within manuscript in methods.
9. From Table 1, it is remarkable that 53% of non-statin users have heart disease and 57% have diabetes, without being on statins. May this represent insufficient treatment related to socioeconomic status, less health consciousness, worse health care in this group, related to worse outcome? Please discuss.

**Reply:** This is a correct observation, but difficult to assess in a retrospective review when primary care management or patient non-compliance was not assessed. We have made a suggestion in the discussion that this may have an untested effect in our review.

10. It is remarkable that 27% of statin users and 30% of non-users have dialysis, whereas the proportions with renal insufficiency are 47% and 23%. Please explain.

**Reply:** We separated out dialysis patients from patients with renal insufficiency who were not receiving dialysis. Patients on hemodialysis are often at greater risk of death and wanted to ensure groups were balanced. Overall though this would make any renal insufficiency 74% and 53% in the groups.

11. Overall, it seems that the prevalence of almost all severe comorbidities listed is much higher in the statin group, yet these patients have a much lower mortality than the seemingly more healthy non-users. What might the reasons be (except a potential statin effect?). Not all conditions are listed – do the authors have data to show on alcohol, substance abuse, immunosuppressive conditions and treatments, liver disease? Please discuss, including the potential role of undiagnosed/underreported severe diseases.

**Reply:** All co-morbid conditions of the patients are listed in table 1 and no other co-morbid conditions were omitted. We have as earlier put in the CCI scores which showed not statistical difference (P=0.15) No HIV patients were present in either cohort. 1 Organ transplant patient was in each group. End stage liver disease usually precludes statin use and so naturally was not part of either group. On a retrospective analysis we can only speculate on a statin effect on a sicker population.

12. Please show data on type of ICU patient / reason for admission (surgical patient, medical patient, severe infection etc.) in Table 1, if available.

**Reply:** have added medical/surgical patient. Sepsis is usual reason for ICU admission and difficult to break out other than by APACHE score

13. References: #5 and #17 are duplicates by mistake.

**Reply:** Thank you for seeing this and corrected.

**Reviewer 2:**

1. the definition of cases and controls is not clear:
Case patients ICU were admitted at the onset of candidemia but controls developed candidemia within an ICU (= after ICU admission?)
comorbid conditions of matching: could you be more specific?
- the common (cases and controls) criteria of inclusion could be pooled in the beginning of "definitions" chapter? Then, what is distinguished cases and controls; else the criteria of matching.
A chart flow could be more clear?

**Reply:** We have clarified the definitions that the onset for all statin/non-statin patients had to have occurred during their ICU stay. With regards to the matching, a flow chart has been made for determining statin and non-statin patients.

2. in the statistical analysis:
-Why to neglect the matching in bivariable comparison?
- In the conditional logistic model, you have included the variables with p-value <0.1 (multivariable comparisons of main characteristics) or <0.05 (association with mortality): Why?
-in what way were selected the sample of 30 controls

**Reply:** We would like to clarify. We did not ignore matching. We calculated p-values in Table 1 using non-conditional statistical tests. However, the primary bivariable comparisons in Table 3 (models 1-6) all accounted for matching. We have changed the methods to express this. We thank the reviewer for this comment. We have also now re-run the analysis and tested each variable in the model based on whether it had the largest impact on the OR for statin exposure. This is based on a comment from reviewer 1.

3. Lastly, the conclusion of your abstract "statins appear to provide a survival benefit in candidemia" is more optimistic, the statins exposure was not associated with a significant reduced mortality after adjustment for the APACHE2 score.

**Reply:** We have clarified that there is a suggestion, rather than have provided a benefit

**Reviewer 3:**

1. In their abstract and conclusion the authors indicate their is an association between statin use and mortality despite the insignificant p-value (p = 0.22). While the lack of a statistically significant finding is likely a result of the small sample size, the authors need to make sure that their interpretation is supported by their results.

**Reply:** You are correct, especially with regards to the confidence intervals on multivariable analysis. We have modified as suggested by reviewer 2.

2. Table 2 contains an asterisk (*) in the title that is not defined.
**Reply:** The asterisk in Table 2 is for mixed candidemia. I think you meant the asterisk in table 3 and this is for variables that could not be included in multivariable model and I have included this statement under the table.

3. The authors seem to go back and forth between case-control and matched cohort as they describe their study. This is not a true case-control study since the outcome (mortality) was not used to classify the groups. The authors need to provide a clear and consistent description of this study.

**Reply:** agree, please see Reviewer 1 Q6. We have revised this throughout the paper.

4. The authors are encouraged to better describe how the two cohorts were matched. Matching on co-morbid factors is very vague. Did the authors use a composite score (i.e. Charlson) or were a set of individual co-morbidities used? Either way, please provide a clearer explanation

**Reply:** Please see reviewer 1 Q2.

**Reviewer 4:**

1. The authors have used a matched cohort design although at the end of the ms they refer to it as matched case-control study. The terms "cases" and "controls" should not be used here but rather "exposed" and "non-exposed". There is no clear description of the selection of "non-exposed" group. Although, they say "non-exposed" groups were matched by comorbidities (not sure how), there were significant differences in comorbidities between the 2 groups.

**Reply:** Please see Reviewer 1 Q6. We agree and have renamed. For matching see Reviewer 3 Q4.

2. The study is underpowered to detect a significant difference. There is no sample size calculation

**Reply:** To isolate an effect of candidemia alone, the exclusion criteria were strict to exclude other causes of sepsis in patients with candidemia that we did not want to evaluate. As you can see, less than 6% of 420 patients over 5 years with candidemia were on a statin at time of their sepsis. This would be difficult to power in a retrospective way. Despite the low numbers, this is determined in a general outcomes and was designed to determine a clinical effect.

3. Although the results of multivariate analysis were non-significant (OR 0.2 (0.02, 2.4) with possible harm with statin in the 95%CI, the authors talk about a benefit of statins in candidemia

**Reply:** see Reviewer Q3

4. The references are outdated. Many studies and systematic reviews have been
published about the topic

Reply: Updated as per reviewer 1 Q1.

5. manuscript needs copy editing

Reply: have addressed all issues.

Editor:

Added University of Maryland as the IRB who reviewed the protocol in the methods section.