Reviewer's report

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

Version: 1 Date: 16 February 2010

Reviewer: Reimar W Thomsen

Reviewer's report:

Thank you for giving me the opportunity to review this interesting 4-year cohort study of the association between statin use and 30-day survival in patients with bacteremia in the ICU. There is very limited data on this topic and the study presents interesting results, although sample size may be considered too small for the advanced regression analyses used, and unmeasured healthy user bias may threaten validity of the results. Writing is very good and succinct.

Major revisions:

Introduction:

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:


Novack V, Eisinger M, Frenkel A, Terblanche M, Adhikari NK, Douvdevani A, Amichay D,


Methods:

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.

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.

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.

Results and Discussion:

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.

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.

7) I 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.

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.

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.

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.

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.

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

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

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests