Author's response to reviews

Title: Association of pre-transplant statin use with graft function in kidney transplant recipients

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Author's response to reviews: see over
1. The use of anti-hypertensives especially ACEi/RBs in the pre and post-operative period is not clearly stated. This needs to be clarified as these drugs in the early post-operative period could influence early graft function.

All anti-hypertensive agents were ceased prior to transplantation and avoided during the first two post-operative weeks. This information has been added to the Methods section (Page 8).

Pre-transplant anti-hypertensive medications in both the donors and recipients were not recorded, such that differential pre-conditioning effects of these agents on subsequent ischaemia-reperfusion injury in the statin and non-statin users could not be excluded. This limitation has now been acknowledged in the Discussion (Page 14).

2. the use of dopamine/inotropes in the post operative periods also needs to be clarified for the reasons stated above

Dopamine and other inotropic agents were not administered to any recipient during the study period. This point has been added to the Methods section (Page 8).

3. episodes of rejection need to be recorded as early rejection may present as DGF

The rates of acute rejection were not significantly different between recipients using statins (n=16 [17%]) and those who did not (n=17 [10%]; p=0.17). This information has been added to the revised manuscript (Page 10, paragraph 2).

4. furthermore the cross match/immunological details of the transplants and RPA status in recipients need to be recorded.

HLA mismatch data are already provided in Table 1. All T cell cross matches were negative; this information has been added to the Methods section (Page 6). Unfortunately, current and peak recipient PRA were not recorded. This limitation has now been acknowledged in the Discussion (Page 14).
Reviewer Hallvard Holdaas

1. etiology of ESRD, no Diabetes mellitus?

A total of 11 recipients had diabetic nephropathy as the cause of ESRD (7 in the prior statin user group and 4 in the no prior statin user group). These were grouped along with all other aetiologies that accounted for less than 5% of all ESRD as “other.” Diabetic nephropathy has now been removed from this group and presented separately in Table 1.

2. unnecessary abbreviations, spell out most of the abbreviations

The extraneous abbreviations in Tables 1, 3 and 4 have all now been spelt out.

3. fraction of time?

The expressed unit for ischaemic time “fraction of hours” has been changed to “hours” to aid clarity.

4. There is some clinical data, randomized clinical trails, which disclaim pleiotropic affects of statins on clinical graft parameters, i.e. rejections episodes, although claimed to be effective in experimental models.

The following sentences have been added to the Discussion (Page 13):

“A previously published systematic review by our group of 5 randomised controlled trials found no significant effect of statin use on the risk of acute rejection in renal transplant recipients (relative risk 0.61, 95% CI 0.32-1.16). Data were not available to evaluate the effect of statins on DGF.”
Reviewer: marcelo santos sampaio

1. In my opinion, authors should study deceased and living donor as a separate population. It would be informative to have the present of DGF in living and deceased donor transplants.

Table 2 has now been updated to separately show graft function after transplantation according to donor type (DBD, DCD and living donor). However, as mentioned in the last line of the Results section, the small number of kidneys donated after cardiac death precluded a meaningful regression analysis stratified by donor type.

2. It is important to define more precisely pre transplant therapy. As the majority of recipients did use atorvastatin this group should be analyzed in separate. No statin vs atorvastatin plus other statins.

The rates of delayed graft function in patients receiving atorvastatin vs those receiving other statins have now been added to the Results section (Page 10).

3. Adjust the sentence on page 8: ND-DGF and pooled results “tended” to be higher in statin users. The P-value was 0.225 and 0.14, respectively, defining no difference.

The sentences have been corrected in accordance with the Reviewer’s recommendation.

4. Title should be modified. The study design cannot answer the proposed question.

The title has been changed to, “Association of pre-transplant statin use with graft function in kidney transplant recipients.”

5. I lack in the discussion some mention of similar clinical studies exist in the literature, and if other authors have examined the pleiotropic effects of statins in kidney transplant, even if not directly related with DGF.

The following sentences have been added to the Discussion (Page 13):

“A previously published systematic review by our group of 5 randomised controlled trials found no significant effect of statin use on the risk of acute rejection in renal transplant recipients (relative risk 0.61, 95% CI 0.32-1.16). Data were not available to evaluate the effect of statins on DGF.”
5. It is important to clarify the dose of statins given to the mice in the mentioned experimental studies and if they are comparable to the doses usually given to treat hypercholesterolemia.

This point has been added to the Discussion (Page 11).

Minor essential revisions

1. The methodology was not well described in the abstract
   a. Cohorts should be defined. This has been done.
   b. Mention that deceased and living donors were included in the study: This has been done.
   c. Statistical method has to be defined This has been done.
   d. Cofounders used to adjust the association: This has been done
   e. OR for ND-DGF need to be included as it is one of the study outcomes. We have not added this extra detail to the results section of the abstract since statin use was dropped from the multivariable logistic regression model during stepwise backward regression. Furthermore, since analyzing the outcomes of D-DGF alone and D-DGF pooled with ND-DGF did not yield statistically significant findings, it follows that the results for ND-DGF alone were not statistically significant.
   f. Conclusion should be limited to the first sentence. The second sentence has now been deleted.

2. page 8, a more precise dose of Atorvastatin should be reported. Also add mean dose for the other statins. This information has now been provided in new Table 2.
3. define in the results the cofounders used in each multivariate model. The variables included in the multivariable models have already been specified in the Methods section (Page 8). We do not believe that they need to be repeated in the Results section.
4. in the limitation, mention that statin was only given to recipients, and that the results may reflect an effect only in the reperfusion mediated kidney injury. The following sentence has been added to the limitations section of the Discussion (Page 14): “Since statins were only administered to recipients, the current result might only reflect an effect in the reperfusion mediated kidney injuries.”