Author's response to reviews

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

Authors:

Janske Reiling (janske_reiling@hotmail.com)
David W Johnson (david_johnson@health.qld.gov.au)
Peter S Kruger (peter_kruger@health.qld.gov.au)
Peter Pillans (peter_pillans@health.qld.gov.au)
Daryl R Wall (daryl_wall@health.qld.gov.au)

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RESPONSE TO REVIEWERS

RESPONSE TO EDITOR

1. Ethics and consent statements

-The ethics and consent statements you added in an earlier revision of your manuscript, 'Data collection for the study was approved by the Princess Alexandra Hospital Research Ethics Committee and individual consent was obtained from all transplant recipients' does not appear to be present in the latest version. Please include this in the revised manuscript.

This has been done (Page 7 Paragraph 1 Line 1).

Reviewer: marcelo santos sampaio sampaio

Major Concerns:
1. Authors’ definitions of delayed graft function are not usual. The most accepted definition of delayed graft function is the need of dialysis in the first week after transplant. Authors used the need of dialysis in the 72h after transplant. Using an unusual definition brings difficulty when comparing authors’ data to other studies. Also, redefining the outcome definition may change study results. Moreover, non-dialysis delayed graft function has no common definition in literature, and just a few studies have used it. Authors should discuss the different ways do define the outcome based on creatinine reduction, so the readers may not get the impression that this is the common definition. One of the best definitions of delayed graft function based in the creatinine decrease was the one used by Boom H (Kidney Int.) and Moore J (transplantation) in their manuscripts. These authors defined delayed graft function as failure of serum creatinine to decrease by at least 10% daily on 3 successive days during the first week post-transplantation. The one day definition may include an isolate and transient intercurrence. I would suggest the use of these commonest definitions, and recheck outcome ratios and association with statins. Otherwise, at least include a comment in the discussion about the different definitions in the literature.

The following paragraph has been added to the Discussion:

“One of the challenges of the present study related to the definition of DGF. There are at least 18 unique definitions of DGF employed in the literature (Yarlagadda 2008). The one that is used most frequently is the need for dialysis post-transplantation, although the specified timeframe in which dialysis occurs is variable. The need for dialysis within 72 hours after transplantation is the definition used by the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA; www.anzdata.org.au) and was therefore employed in this study. However, given that such a conservative definition potentially excludes a significant number of patients with less severe forms of DGF, a sensitivity analysis was performed to include these patients using a broader definition. Govani et al devised and validated the creatinine reduction ratio at post-operative day 2 (CRR2) <30% as a simple, objective criterion for early diagnosis of DGF (Giovani 2002). Both Rodrigo et al and Vilar et al subsequently demonstrated that patients with a CRR2<30% (ND-DGF) had a significantly lower 5 year graft survival than patients with IGF (rodrigo 2004, vilar 2010). Nevertheless,
regardless of whether the need for dialysis post-renal transplantation was considered alone or in combination with the CRR2 criterion, statin therapy was not associated with DGF in the present study.”

2. I insist that authors should try to analyze in separate deceased and living donor (item 1 of the previous revision). Results should be shown in table 4 and 5. It is very difficult to adjust results in a similar way to deceased and living transplants. By doing like this no interaction term is needed. Kidney donated after cardiac death can be pooled together with brain death, or just add a note that deceased analysis included only brain death donor transplant as the few number of donation cardiac death do not allow a adjusted analysis.

Sensitivity multivariable logistic regression analyses have been performed separately for DBD and living donor transplants. The results have been added to the Results section (Page 10 Paragraph 4). Multivariable logistic regression analyses were not able to be performed for the small number of kidneys donated after cardiac death (DCD). This has also been noted in the Results section (Page 11 Paragraph 1). DGF rates are quite different between DBD and DCD transplants, such that it is inappropriate to lump them together if no interaction term is being included. The sensitivity analyses did not alter the findings or conclusions drawn from the study.

3. Authors define OR by multivariable logistic regression analysis. They describe backward stepwise model elimination until the most parsimonious model was identified. The stepwise model may include in the final model some of the co-variables used in the initial model according to a pre-defined p-value, or it can be done by excluding variables according to its significance after running the initial model and re-running the new model. This last model has the interference of the researcher, as he can choose variables and can keep the ones he feels are important for the adjustment despite of the p-values. It has to be better specified in the methods how authors did it. Also, in either way, variables may change when studying different outcomes (D-DGF, ND-DGF). The final variables used to adjust the OR in each model have to be specified. I suggest including a line in the bottom of table 4 and 5. I just could find in methods (page 8) the variables initially included in the model, not actually the description of the variables used in the final model (please refer to minor revisions #3 in my previous revision)

The backward stepwise elimination method was based on a p value cut-point of 0.2 (without interference from the researcher). The Methods have been modified as follows: “The independent predictors of DGF were evaluated by multivariable logistic regression using backward stepwise elimination based on a p value cut-point of 0.2 until the most parsimonious model was identified.”

Only measures resulting in statistical significance in the final adjusted regression model are shown in table 4 and 5 (although statin use was obviously forced to remain in the model). The final variables included in the multivariable models are now listed at the bottoms of Tables 4 and 5.

4. Still regarding the variables used to adjust the model, the length of hospitalization cannot be used here. Length of hospitalization is in general an
event defined by delayed graft function, and not vice-versa. Authors acknowledge it in their introduction section of the manuscript. Also, as the objective of the study is to define risk of using statin the variable for it should not be dropped from the model even if not significant in univariate analysis.

Length of hospitalization has now been excluded from the model. The adjusted odds ratios for statin use are displayed in Tables 4 and 5.

5. On tables 4 and 5 the following should be revised:
   a. N from table 5 (249) is smaller than in table 4 (252), please verify and explain. Maybe create a figure showing the intersection between the different definitions (e.g. as done in Moore J et al in Transplantation). It may be related to the inclusion of variables in the mode with missing values.

   The difference did relate to missing values (mostly pertaining to length of hospitalization). After rerunning the analyses following exclusion of length of hospitalization from the model, the N value for both Tables 4 and 5 is now the same (256).

   b. In BMI OR cannot be zero. <18.5 group has probably not enough N to be analyzed. Please explain the inclusion of p-value of 0.23 in table 4. In table 5 p-value or CI is wrong in <18.5 group. Also, explain 0.02. As explained above use of length of hospitalization as a cofounder should not be used.

   Length of hospitalization was dropped from the model, which greatly improved model stability. Tables 4 and 5 have now been modified to only show statin use and statistically significant variables in the final adjusted regression model.

   c. I am very surprised that the cold ischemia was not a risk factor for delayed graft function. I believe that is was caused by analyzing in the same group living and deceased donors. Please verify and comment.

   Although warm ischaemic time was found to be a risk factor for delayed graft function, cold ischaemic time was not observed to be a risk factor for delayed graft function (either D-DGF or D-DGF + NDE-DGF) in all kidney transplant recipients, DBD kidney transplant recipients or living donor kidney transplant recipients.

6. Missing data cited in the methods should be specified in methods and not only in table 1. Authors can mention that X% of data from age is missing.

   The % data available has now been indicated for each variable.

7. Table 2 is not necessary.
   I suggest adding in page 9 median dose of statin used in deceased, living donor and overall recipients, in the place of the sentence “97% of ….or less Table 2”. I think it would be equally informative, and avoid inclusion of one more table to the manuscript.

   The information provided in Table 2 had been previously requested by other reviewers (including Dr Sampaio). The current number of tables in the manuscript (5) is not excessive, particularly considering that there are no figures.
8. Title: use “delayed graft function” instead of “graft function”

The title has been changed in accordance with the Reviewer’s request.

Minor Concerns:
1. I suggest adding in the background percent of DGF in living and deceased donor found in the literature and comment the different risk factors associated with increased risk of delayed graft function according to donor type.

Paragraphs 1 and 2 of the background (Page 5) have been modified according to the Reviewer’s suggestion.

2. As a consent form was collected, please mention IRB approval.

The following statement has been added to the Methods section (Page 7 Paragraph 1):

“Data collection for the study was approved by the Princess Alexandra Hospital Research Ethics Committee and individual consent was obtained from all transplant recipients.”

3. In statistical analysis change “number” to “percent” and exclude % in parenthesis. Define interquartile range. 25-75percentile? As it is a non-randomized study it is difficult to believe that a variable can have a normal distribution. Maybe the age, race? Please indicate the test used to calculate the p-values in table 1. Use a symbol as an indicator and give the test name in the bottom of the table.

Data have been presented as number (%), so we have not changed this description in the Methods section. Interquartile range was defined as 25th-75th percentile and has now been clarified in the Methods section (Page 8 Paragraph 1 Line 2). Whether the distribution of a given variable is normal or not normal is not influenced by whether or not the study design is randomized. The statistical analyses used have already been described in the Methods section, as follows: “Comparisons between groups were made by χ² test for categorical variables, unpaired t-test for continuous normally distributed variables and Mann-Whitney test for continuous variables not normally distributed.”