Author's response to reviews

Title: Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition.

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Version: 3 Date: 4 November 2011

Author's response to reviews: see over
Leiden, 25 October 2011

Dear Dr Chap,

We would like to thank you for giving us the opportunity to react to the comments/advices of the reviewers and the chance to resubmit an improved version of our manuscript: ‘Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition.’

Furthermore we would like to thank the reviewers for their constructive criticism and helpful comments, which we used in the result and discussion section of the article. We sincerely hope that these answers and adjustments will appeal and that you would reconsider the article for publication in your journal.

On behalf of all the authors,

Marielle Schroijen
Reviewer: Behrooz Broumand

Thank you for reviewing the article entitled: *Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition*. We thank the reviewer for the constructive comments and interest in our work.

Comment:

*It is wrong to label Diabetes as a primary renal disease? it should be changed to diabetic nephropathy. The main problem is the authors have not provided a clear definition of Diabetes as a co-morbid condition. I copy and paste the authors "The diagnosis was based on the opinion of the physician, reflecting common clinical practice. We can not exclude that some patients could have been misclassified, especially in patients with diabetes as a co-morbid condition and a primary diagnosis of renal vascular disease." Apart from above problem how is possible in patients with ADPKD and DM we exclude the possibility of DN without biopsy if they develop ESRD. There are many other shortages that the authors themselves explained and this decrease the value of their conclusions. Plus many assumption like their glycemic control should have been comparable?*

I:

We agree with the reviewer that renal biopsies are the reference standard to confirm whether diabetes is indeed the primary cause of the nephropathy. However, a renal biopsy is an invasive procedure with a potential risk of complications and is therefore often not performed in a routine clinical setting. The term diabetic nephropathy is closey linked to a pathological diagnosis, (*Cohen Tervaert TW; J Am Soc Nephrol. 2010 Apr;21 (4): 556-63*). Because we do not have a pathological diagnosis in most of our patients we preferred to use the term diabetes as primary renal disease and diabetes as a co-morbid condition to make a clear distinction between a pathological and clinical diagnosis of patients with ESRD and diabetes mellitus.
Renal biopsies are the reference standard to confirm whether diabetes is indeed the primary cause of the nephropathy. However a renal biopsy is an invasive procedure with a potential risk of complications and is therefore often not performed in a routine clinical setting.

II:
We assumed that the greatest risk of misclassifying is in patients with diabetes as a co-morbid condition and a primary diagnosis of vascular renal disease. In such cases it can not be excluded that diabetes may have contributed largely to the renal failure. However exclusion of patients with diabetes as a co-morbid condition and a primary diagnosis of renal vascular disease did not materially influence the study results.

III:
We agree with the reviewer that in this study of Catalona et al routine biopsies were not performed, so the possibility of diabetic nephropathy can not be excluded in patients with diabetes and a primary diagnosis of adult polycystic kidney disease. However, the conclusion is that diabetes mellitus has a very strong impact on survival even if it is not the primary cause of ESRD.

IV:
Glycemic control of our patients was not documented. Treatment of NECOSAD patients was provided according to (inter)national guidelines, and these guidelines do not differ for patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition, so it is unlikely that treatment for diabetes would have differed between the groups.
Reviewer: Chiu-ching Huang

Thank you for reviewing the article entitled: Survival in dialysis patients is not different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. We thank the reviewer for the constructive comments and interest in our work.

Comments: Major Compulsory Revisions
This multicenter prospective cohort study (NECOSAD) gives interesting information of Dutch patients, comparing survivals of those with diabetes as primary renal disease or diabetes as a co-morbid condition. The most important message is patients with either diabetes as primary renal disease or diabetes as a co-morbid condition have increased mortality risks when compared to non-diabetic patients. Contrary to the general belief that patients with diabetes as primary renal disease may have inferior survivals than those with diabetes as a co-morbid condition due to more severe end-organ damage in the former group. The manuscript is well written with clarity. The limitation of the study is well described in discussion.
Unfortunately, there is confusion about the tables. The content of Table 2 and Table 3 (page 8) did not match the description in the text. Moreover, Table 4 (page 9) which was mentioned in the text was not found in Table section (page 17-18). There appears one table is missing. The authors must revise their tables.
The other concern I have about this study is number of patients with diabetes as primary renal disease (N=281) and diabetes as co-morbid condition (N=107) were relatively small.

Answers:
We thank the reviewer very much pointing this inconsistency in numbers of tables. We apologize that these tables were not correct. Our tables had been revised accordingly.

We agree with the reviewer that the number of patients with diabetes as
primary renal disease (N=281) and diabetes as co-morbid condition (N=107) were relatively small. However the total number of patients included in the cohort is 1853. That can considered to be a reasonable amount of patients for such a cohort. The percentage of patients with renal replacement therapy and diabetes is normal for a European study. The uncertainty in effect estimates accompanying the relatively low number of diabetes patients is reflected in the width of the confidence intervals.

**Comments Minor Essential Revisions:**

1. Page 16, Table 1. I suggest you to add p values, denoting the significance of differences of variables between these three groups.

We thank the reviewer for his comment. In addition to the confidence interval we provided p values in table 1.

2. Page 8: Please describe how many patients switched modality between HD and PD.

In the result section we mentioned how many patients switched modality between HD and PD. We did not use these data in our analysis because our analysis is an intention to treat analysis. In the end, as we all know, it is not allowed to predict the future from the future.

We included the following paragraph in the result section: Page 9, Line 6-10, section peritoneal dialysis.

Five hundred and fifty five patients had no diabetes, 102 patients had diabetes as primary renal disease and 27 patients had diabetes as a co-morbid condition. After 3 months a few patients switched to hemodialysis; 15 patients without diabetes, 3 patients with diabetes as primary renal disease and none of the patients with diabetes as a co-morbid condition.

Furthermore Page 9, Line 16-20, section hemodialysis.
Nine hundred and ten patients had no diabetes, 179 patients had diabetes as primary renal disease and 80 patients had diabetes as a co-morbid condition. After 3 months a few patients switched to peritoneal dialysis; 39 patients without diabetes, 3 patients with diabetes as primary renal disease and 5 patients with diabetes as a co-morbid condition.

3. Page 9, line 15-17: You mentioned further adjustment for risk factors and co-morbidities did not materially influence the study results in HD and PD patients. I urge you to report the numbers of hazard ratio and 95% CI of this model in the text.

Based on these comments we added the following paragraph to the result section: Page 9, Line 25 and Page 10, Line 1-5.

After these adjustments the HR in PD patients with diabetes as primary renal disease was 2.9 (95 % CI 2.1, 4.0) and 1.2 (95 % CI 0.7, 2.3) for PD patients with diabetes as a co-morbid condition compared to the reference group. The HR in HD patients with diabetes as primary renal disease was 1.7 (95 % CI 1.3, 2.3) and 1.9 (95 % CI 1.3, 2.7) for HD patients with diabetes as a co-morbid condition compared to the reference group.

4. Page 9, line 6-10 and Page 11, line 13-15: You mentioned “Mortality risk in PD patients for diabetes as primary renal disease was increased compared to patients without diabetes, whereas this was not the case in PD patients with diabetes as co-morbid condition.” This insignificance may also be possible due to relative small number of PD patients with diabetes as co-morbid condition. This possibility needs to be mentioned in the section of Discussion.

We agree with the reviewer that this insignificance may also be possible due to relative small number of PD patients with diabetes as co-morbid condition. We included the following paragraph in the discussion section: Page 12, line 17-18.
The fact that we could not found a difference in PD patients with diabetes as a co-morbid condition could be due to limited power.

5. *Number of patients with diabetes as primary renal disease (N=281) and diabetes as co-morbid condition (N=107) were relatively small in this study.*

*Please clarify how many patients in each group received either PD or HD? I also suggest you to show number of patients left in each follow up year of each three groups in Fig A and Fig B.*

We thank the reviewer for his comment. We clarified how many patients received PD and HD. We already included a paragraph in the result section: see comment and answer mentioned at point 2. Furthermore we showed the number of patients left in each follow up year of each three groups in figure A and B.