Author's response to reviews

Title: Association of blood pressure with decline in renal function and time until the start of renal replacement therapy in pre-dialysis patients: a cohort study

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Author's response to reviews: see over
Leiden, July 14, 2011

Dear editor,

Recently we received your email, dated the 20th of June 2011, concerning your decision on our manuscript ‘Association between blood pressure and decline in renal function and time to start of renal replacement therapy in pre-dialysis patients: a cohort study’. We are pleased that you are willing to reconsider our manuscript.

We would like to thank the reviewers for their constructive comments. At the end of this letter we give a point-by-point response on the questions/comments of the three referees and the editor. Following the questions from the reviewer in italic is our response, including referral to page and line number in the revised document. The revised version of our manuscript is uploaded as an additional file, with additions in blue and deletions made visible by strikethrough.

We hope that the given answers and the changes we have made are sufficient for publication of the manuscript in BMC nephrology.

With kind regards,
Also on behalf of all co-authors,

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Referee 1: Nisha Bansal

Major revisions:

1.) *Is there a difference in rate of progression among those with more eGFR measures versus those with only 2 measures – patients with 3 vs. 9 measures for example will have very different slope estimates. There may be a bias in those who have more eGFR measurements during the follow-up period. Maybe this can be compared in a sensitivity analysis.*

→ It is an interesting comment that the rate of decline in renal function (eGFR) may differ between patients with for example 3 eGFR measurements and patients with 9 eGFR measurements available. Further analyses showed that the mean (SD) decline in renal function did not differ much between the quartiles of number of available eGFR measurements, consisting of patients with 2-6, 7-9, 10-13 and 14 or more eGFR measurements. Therefore, the effect of bias seems small. For this reason we chose to add only a sentence about this information to the decline in renal function section of the results (page 12, line 9-12) instead of adding a complete sensitivity analysis.

2.) *Do the authors have any information on the previous rate of eGFR decline in these patients? If possible, this would be important to adjust for as those who declined more rapidly to this point are more likely to need RRT sooner.*

→ We agree with the reviewer that patients who declined more rapidly before the start of pre-dialysis care are more likely to have an earlier start of renal replacement therapy (RRT). Therefore, adjustment for factors influencing prognosis, such as the renal function decline before pre-dialysis care, is important. However, as was already mentioned in the discussion (page 20, line 2-4), too few eGFR measurements prior to the start of RRT were available in our cohort and therefore adjustment for rate of decline in renal function was not possible. However, baseline renal function (eGFR) was available and we adjusted for this.

3.) *I would be interested in seeing the results of the sensitivity analysis using a longer duration of follow-up time – the authors state that the results were diluted but it is not clear what length of follow-up time they used and how their results changed. The short length of follow-up may be an issue. For the patients that started RRT within 1 year, the mean time to RRT was 145 days, suggesting that*
These patients were sicker when they started pre-dialysis care and blood pressure level may have not have changed their outcome significantly.

The reason for choosing one year of follow-up is explained in the discussion of the manuscript. In our opinion blood pressure changes during pre-dialysis care may bias the association between baseline blood pressure and progression of chronic kidney disease (CKD) when using complete follow-up. Therefore, we chose to use one year of follow-up for the main analyses. We do agree that only stating that results were diluted when using complete follow-up (length of follow-up is from start of pre-dialysis care until RRT, mortality or January 1st 2008) is not sufficient. Therefore we added the results from the continuous sensitivity analysis using complete follow-up (page 14, line 18-21).

It is possible that the patients who started RRT within 1 year had a worse prognosis when they started pre-dialysis care. However, we don’t think that blood pressure level therefore has not changed their outcome significantly. First, we adjusted for possible other prognostic factors and the results remained strongly present (page 19, line 17-23, and page 20, line 1-2). Second, almost all patients were referred by nephrologists and one of the inclusion criteria of the study was the expectation that patients will start RRT within one year. This may give an indication that prognosis is similar between patients.

Minor revisions:

1.) For Table 1, the authors should show the characteristics for the final study population (n=436) rather than the n=508.

For the analysis with decline in eGFR as outcome, 436 pre-dialysis patients were included and for the analysis with time to start of RRT as outcome, 508 patients were included. Therefore, Table 1 represents the baseline characteristics for the largest study population used in our statistical analyses (n=508). In the first paragraph of the results section we furthermore highlighted the characteristics that differ between patients with an available rate of eGFR decline (n=436) and patients without an available rate of eGFR decline (n=72).

2.) It is unusual that the mean eGFR at the start of dialysis was the same in both the ‘above’ and ‘below’ target groups (8.2 ml/min/1.73 m²). Is this correct? When was the eGFR measured in relation to starting dialysis?

For calculating this mean eGFR, the closest measurement of eGFR to the
date of starting RRT was used. However, after further analyses we discovered that the time between this measurement and the start of RRT was twice as long for patients below the target compared to patients above the target. This leads to bias in the mean (SD) eGFR and could explain why eGFR at start of dialysis was similar in both groups. Therefore, we chose to only select the eGFR measurements that were measured 2 weeks or less before the start of RRT. This means that not for all patients an eGFR at start of RRT was available. The mean (SD) eGFR for patients below the target is 6.7 ml/min/1.73 m$^2$ and for patients above the target 8.2 ml/min/1.73 m$^2$. We changed these numbers in the results section of the manuscript (page 13, line 11-13).

3.) There was an equal number of PD and HD patients in the study – this may not be generalizable to the U.S. population. This should be included as a limitation in the study.

   ➔ This is indeed a limitation and therefore we added this limitation to the discussion (page 18, line 17-19).

4.) How many patients declined dialysis? Were there any patients who died from uremia? How was this handled in the analysis?

   ➔ Information about whether patients declined the start of dialysis was not available. However, based on the fact that these patients were all referred to specialized pre-dialysis outpatient clinics aiming to prepare patients to start RRT we think that only few patients declined dialysis in this specific population. Information about causes of death during the first year of follow-up was only available for 18 out of 24 patients who died during the first year of follow-up. Using data of these 18 patients, 1 patient died from uremia. If we use the complete follow-up, in total 10% died from uremia. Patients who declined the start of dialysis or who died, were included in all analyses and were used as censored events in the analysis with time to start of RRT as outcome (mentioned in the methods, page 10, line 6-7).

Referee 2: Okada Tomonari

Revisions:

1.) I think that the information how to obtain the data of clinic blood pressure is insufficient. The method of blood pressure measurement should be explained.
Indeed, the information on how blood pressure was measured is relevant in this study. However, blood pressure measurements were obtained from medical charts of the patients, and therefore we could not exactly describe how blood pressure was measured in each individual patient (described on page 7, line 20-22). However, in Dutch hospitals blood pressure is most often measured with a blood measuring device dependent on cuff occlusion of the arm, with the patients in a sitting or lying position. We added this extra information to the measurements and definitions section of the results (page 7, line 22-23, and page 8, line 1).

2.) It is shown that the sensitivity analysis found similar significant associations between blood pressure and renal progression after adjustment by proteinuria, hemoglobin, and baseline eGFR. However, these variables are very important confounding factors for the multivariate analysis. If possible, GFR decline and HR after adjustment by these variables should be also reported in the article.

2.) It is shown that the sensitivity analysis found similar significant associations between blood pressure and renal progression after adjustment by proteinuria, hemoglobin, and baseline eGFR. However, these variables are very important confounding factors for the multivariate analysis. If possible, GFR decline and HR after adjustment by these variables should be also reported in the article.

We chose to report the adjustment for proteinuria, hemoglobin and baseline eGFR as a sensitivity analysis, because these variables were not available for all patients. According to the comment of the reviewer we added the adjusted continuous results to the sensitivity analyses section of the results (page 15, line 1-4).

3.) In the discussion, the author suggested the influence of arterial stiffness or pulse pressure on decline in renal function. However, this study has not shown the association between pulse pressure and renal prognosis. The previous observational studies regarding the association between arterial stiffness and renal prognosis are very limited. If possible, the renal risk of increase in pulse pressure should be examined. I think that the explanation for the association between blood pressure and renal prognosis is weak. In addition, the suggestion of ‘Reduced blood supply to the kidney causes accumulation of uremic substances and influences progression of renal disease.’ seems not to be scientific. If it is true, the references supporting this suggestion should be added.

We agree with this reviewer that pulse pressure is an interesting blood pressure measure. However, for these analyses we chose not to include pulse pressure, because this blood pressure measure is not incorporated into the current clinical guidelines for pre-dialysis care (DBP <80 mmHg and SBP <130 mmHg). However, in the discussion of the manuscript we wanted to highlight that
arterial stiffness can be a possible biological explanation for the effect of high systolic blood pressure on an accelerated decline in renal function. Therefore, in the discussion we mentioned pulse pressure, which is a marker for arterial stiffness. To support this possible biological explanation, we investigated briefly whether pulse pressure was associated with decline in eGFR and time to start of RRT. On a continuous scale indeed it was true that increasing pulse pressure was associated with a faster progression of CKD and therefore we mentioned this in the discussion. However, in line with our main focus on the guidelines we chose not to report the exact results of these analyses. Furthermore, we extended the biological explanation for the association between blood pressure and renal prognosis and added a reference (page 20, line 13-23 and page 21, line 1-10).

4.) If possible, the study population receiving erythropoietin stimulating agents should be added. In Table 1, the definition of anemia in co-morbidities should be added.
   → To avoid confusion about the definition of anemia, we added this definition to the baseline characteristics table (Table 1, page 29).
   The goal of table 2 was to indicate the prescribed anti-hypertensive medication, therefore we did not include erythropoietin stimulating agents use to this table.

5.) Recently one large interventional study (NEJM 2010; 363: 918) showed no significant effect of intensive blood pressure control on CKD progression. This study population is mainly stage 3 CKD. In stage 4 and 5 CKD, the significance of intensive blood pressure control is uncertain. I think that more discussion is necessary for the interpretation of the positive results in this study and the negative results of the previous interventional studies.
   → This is a useful suggestion and we included a comparison between the results of these trials and our results to the second paragraph of the discussion (page 17, line 13-23, page 18, line 1-16).

Referee 3: Kunitoshi Iseki

- Unfortunately, other predictor of progression such as proteinuria was not evaluated.
   → Our aim for this specific study was to investigate with an etiological approach,
whether blood pressure is a risk factor for progression of CKD. Therefore, we adjusted for confounding risk factors such as proteinuria. Indeed it is also very interesting to investigate proteinuria as an independent risk factor for progression of CKD and a couple of months ago we started this investigation.

- For this reviewer, it is interesting to see the incidence of RRT is much larger than death rate which is contradicting the previous report (Keith et al. Arch Intern Med 2004).

→ We agree with the reviewer that the mortality rates in the study performed by Keith et al are not comparable to our mortality rates. However, the cohort of Keith et al contains CKD stage 4 patients who are much older than our pre-dialysis patients (73.6 vs 65.0 years) and represents less white patients than our cohort (78% vs 96%). Furthermore, one of the inclusion criteria of the PREPARE study was the expectation that patients will start with RRT within one year. Therefore, our cohort is a selective group of patients who already survived to the start of pre-dialysis care. These differences between the cohorts could explain the lower mortality rates in our cohort.

- Control of BP was poor despite care by specialists. Why was this? It would be interesting to refer the previous report from Japan (Nakayama M, et al. Clin Exp Nephrol 2010).

→ 89% of the pre-dialysis patients in our cohort have a blood pressure above the guideline of <130/80 mmHg which is a large proportion. It is very difficult to reach the blood pressure treatment target, which is in line with results of the MASTERPLAN study (van Zuilen, J nephrol 2008). In contrast, Nakayama et al showed that blood pressure was controlled well in CKD patients. However, this cohort mainly represents patients with CKD stages 1-3 (77.9%). It can be reasoned that blood pressure control is easier to achieve in patients with an early stage of CKD (stage 1-3) compared to patients with advanced stages of CKD (4-5, included in our cohort). We added this explanation and the references mentioned to the third paragraph of the discussion (page 18, line 4-8).

Minor revision:

1.) Table 2. Are there any differences in the number of anti-hypertensive drug types between the groups?
An extra sentence with this information was added to the second paragraph of
the results (page 11, line 23 and page 12, line 1-2).

**Editor**

- **All tables should be legible on a single standard page and should not cross over onto a second page.**
- I reformatted the tables to fit on one page, with the assumption that legends may cross over onto a second page.
- **We recommend that you copyedit the paper to improve the style of written English.**
- The manuscript was copy-edited by a native English speaking colleague. This also resulted in little changes in the title of our manuscript.